BRITISH JOURNAL OF TUBERCULOSIS
AND DISEASES OF THE CHEST
Vol. LI. APRIL, 1957 No. 2.

CLINICAL FEATURES OF POLYARTERITIS NODOSA WITH LUNG INVOLVEMENT

BY G. A. ROSE

From the Medical Unit, St. Mary's Hospital, London, W.2

IT is ninety years since polyarteritis nodosa was first described (Kussmaul and Maier, 1866), but until about fifteen years ago it remained a pathological curiosity. Subsequently the clinical descriptions of Grant (1940) and others, and the use of muscle and skin biopsy, have made diagnosis in life a possibility. At the present time in this country about half of the diagnoses are first made clinically, and with greater awareness of the disease this figure could certainly be higher. The condition can no longer be called a rarity, and with the introduction of cortisone and ACTH its early recognition has become of great importance.

The purpose of this paper is to describe the pulmonary manifestations of the disease, since these are unfamiliar and often lead to errors in diagnosis. The material is derived largely from experience gained in a survey undertaken for the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council. This survey was based on a total of 111 proven cases of polyarteritis nodosa under care in nine teaching hospitals during the period 1946 to mid-1953; there was evidence of lung involvement in one-third of the cases. A complete analysis of the results, together with the case histories, is lodged with the Medical Research Council; a copy can be loaned on request.

One of the interesting features which emerged from this study was that the cases with lung involvement appeared in many respects to form a distinct group. It was found that in this group the lung lesions nearly always preceded the appearance of polyarteritis in other organs, and that they produced a characteristic respiratory illness, often associated with eosinophilia. After an interval which might vary from days to years there appeared, usually suddenly, evidence of polyarteritis in other viscera; and thereafter the disease tended to follow a rapidly progressive course. At necropsy the group was characterised by the frequent presence of pulmonary polyarteritis, necrotising and granulomatous lesions in various organs (especially the lungs), granulomatous polyarteritis (sometimes with a giant-cell reaction), and many eosinophils around the arterial lesions. These features occurred rarely or not at all in cases without lung involvement. Detailed evidence in support of this classification has been published elsewhere (Rose and Spencer, 1957). The present paper deals simply with the clinical and radiological problems involved in the diagnosis of polyarteritis nodosa with lung involvement.

(*Received for publication July* 6, 1956.)

Clinical Features of the Respiratory Illness

In cases of polyarteritis nodosa with lung involvement respiratory symptoms are almost always an initial manifestation of the disease, and usually there is an interval of weeks or months before the first evidence of lesions in other organs. Sometimes this interval may be several years, especially in patients with asthma. The disease affects the sexes equally; its incidence increases with age, reaching a maximum in the sixth and seventh decades.

The respiratory illness may start either insidiously or acutely, but generally tends to be progressive and is often fatal. Clinically it presents in three main forms: pneumonia, bronchitis and asthma. At necropsy the lesions are similar in each type of case.

(i) *The Pneumonic Type of Illness*

Case 1 (Case 84 in Medical Research Council Series). A housewife aged 51 years developed right-sided nasal obstruction followed three weeks later by pain, discharge and deafness in the right ear. She attended an ear, nose and throat specialist, who found that the nasal septum was granular and bled easily; he thought that this might be due either to tuberculosis or syphilis. Two months later the patient developed a dry cough, breathlessness, and dull aching pain in the right side of the chest, accompanied by loss of weight. She was admitted to hospital and found to have irregular fever up to 102° F. Physical examination revealed fine râles at the right lung base, and also bilateral iridocyclitis. She had anæmia and neutrophil leucocytosis, and chest X-ray showed a circumscribed opacity in the apical segment of the right lower lobe and also slight infiltration in the left mid-zone. No tubercle bacilli could be found in the sputum, and no lesions developed in a guinea-pig inoculated with mucus aspirated at bronchoscopy. Nevertheless the patient's illness was presumed to be tuberculous, and she was treated with streptomycin and PAS. There was no improvement, and during the following week she developed effusions into the left knee and right ankle, and the urine was found to contain protein, red blood cells and casts. Shortly afterwards she suddenly produced a large amount of sputum and was rapidly asphyxiated. Necropsy showed a ragged abscess cavity ($6 \times 6 \times 5$ cm.) at the apex of the right lower lobe; this had ruptured into the bronchus. Microscopically there was widespread interstitial fibrosis, hæmorrhage and polyarteritis in the lungs, and polyarteritis in the spleen and kidneys; many glomeruli were occluded by microthrombi.

It is not uncommon for patients with this disease to present initially to an ear, nose and throat department. They may show simply pale hypertrophic nasal mucosa, often associated with polypi and sinusitis. But the more characteristic appearance is the nasal or middle ear granuloma, as illustrated by this patient. This lesion does not seem to occur in cases of polyarteritis nodosa without lung involvement; but it does have to be distinguished from neoplasms, tuberculosis and syphilis.

The chest lesions in this patient were radiologically indistinguishable from tuberculosis, and this is often the case. She did however show from the start several features, in addition to the upper respiratory granuloma, which are more frequent in polyarteritis nodosa than in tuberculosis. These included iridocyclitis, anæmia and leucocytosis. Most important of all was the inability

to demonstrate tubercle bacilli. (Negative examinations for tubercle bacilli were recorded on sixty-nine specimens of sputum in the M.R.C. series, including twenty-two specimens from patients with lung cavities.) The appearance later in this case of arthritis and urinary abnormalities made a diagnosis of polyarteritis nodosa very probable, and would have justified "blind" muscle biopsy.

Case 2 (Case 51 in Medical Research Council Series). A 33-year-old housewife attended hospital complaining of pain in the right side of the chest of three weeks' duration. A year previously she had had an episode of left-sided pneumonia, details of which were not available. On examination there were medium and fine râles at the base of the right lung, and also fever (up to 100° F.) and neutrophil leucocytosis. Chest X-ray showed two abscesses, 3 cm. in diameter, in the anterior basal segment of the right lower lobe (Fig. 1A, Plate XIII). Bronchography revealed surrounding bronchiectasis. The abscess failed to resolve with penicillin therapy and was therefore treated by lobectomy. The appearances of the resected lobe resembled fibro-caseous tuberculosis, but no tubercle bacilli could be seen. Two months after the operation the patient developed a hæmorrhagic ulcerating skin rash, conjunctivitis and loss of weight. She was readmitted to hospital and was found to show fever, an E.S.R. (Westergren) of 92 mm. in 1 hour, and the presence in the urine of protein, red blood cells and casts. A clinical diagnosis of polyarteritis nodosa was confirmed by skin biopsy. During the following month new infiltrations appeared in the right upper and middle lobes and the left lower lobe; these broke down to form multiple cavities. During this period the patient developed hypertrophic osteoarthropathy. She was treated with ACTH followed by relatively small doses of cortisone, with dramatic improvement in her general condition and in the skin rash. She was able to go home and do her housework, although continuing to produce about 30 ml. daily of blood-stained sputum. The urine still contained protein and red blood cells. Chest X-ray now showed an enormous cavity in the right lung (Fig. 1B, Plate XIII), although later on this contracted considerably. Repeated examinations of the sputum for tubercle bacilli were all negative. Gradually the blood urea began to rise, and there was progressive enlargement of the spleen and liver. Eventually the patient died of renal failure, four years after the first episode of pneumonia. Necropsy showed many chronic abscess cavities (up to 5×3 cm.) in the right middle lobe, and a solitary abscess in the left lower lobe. There was extensive amyloidosis of the kidney, liver and adrenals, but no evidence of active polyarteritis.

This patient's illness was mistaken at first for chronic lung abscess. However, as is typical of pulmonary polyarteritis nodosa, there was no response to antibiotic therapy. Local resection was followed by spread of the disease both to systemic organs and to new areas of lung. The response to cortisone was interesting in that the patient's general condition improved very greatly despite the increase in size of the lung cavities. The relation of the latter to cortisone is debatable. Neither cavities of this size nor amyloidosis appear to have been recorded before in this disease, either with or without cortisone therapy. Experience of other cases with pulmonary polyarteritis nodosa has shown that non-cavitated lesions tend to resolve under the influence of adequate doses of cortisone or ACTH, a fact which often makes it difficult to identify any specific changes at necropsy in such cases. More experience is needed in the cortisone treatment of cavitating lesions.

CASE 3 (Case 89 in Medical Research Council Series). An 18-year-old girl developed a cough, hæmoptysis, scanty sputum and some loss of weight. Chest X-ray showed " disseminated, apparently tuberculous, lesions, throughout the left lung and in the right upper lobe." She was admitted to a sanatorium and treated by artificial pneumothorax, although it was noted at the time that her general condition was surprisingly good for such extensive disease, and no tubercle bacilli could be found in the sputum. There was fairly rapid healing and calcification of the lesions, and the patient was discharged. The following year there began a slowly progressive impairment of visual acuity, and serial X-rays showed that the heart was enlarging. Three years later she was admitted to hospital for termination of pregnancy because of the " tuberculous " history, and was then found to have malignant hypertension and a raised E.S.R. She died of renal failure a few months later. At necropsy there were caseous masses in the upper lobes and right lower lobe of the lungs; some of the lesions were calcified. No tubercle bacilli could be demonstrated. There was also widespread polyarteritis, mainly granulomatous, in the kidney, mesenteric vessels and pancreas, and small granulomata in the liver.

Here again, as in the first case, the lung lesions were mistaken for tuberculosis. The case also illustrates that even when the lesions appear radiologically to have healed, necropsy may show that there is still extensive lung destruction. Calcification is unusual. The hypertension is attributable to renal involvement (Rose and Spencer, 1957), urinary evidence of which in this patient may well have escaped notice at the time of the original respiratory illness. A possible diagnosis of polyarteritis nodosa should always be considered if a patient with severe or rapidly advancing hypertension is found to have a high E.S.R. or leucocytosis, and any earlier history of respiratory disease in such cases should be carefully reviewed.

(ii) *The Bronchitic Type of Illness*

CASE 4 (Case 93 in Medical Research Council Series). A 40-year-old woman noticed the gradual onset of progressive tiredness, loss of weight, breathlessness, and cough productive of a little white sputum. Examination revealed signs of bronchitis. Three years later she developed asymmetrical polyneuritis and was admitted to hospital. She looked thin and ill; her blood pressure was 190/120, and the urine contained protein and casts. There were râles at the lung bases, and chest X-ray showed multiple small ill-defined opacities throughout both lung fields. No tubercle bacilli could be found in the sputum. White blood counts showed an eosinophilia of up to 2,000/mm.^{3}, and X-ray of the limbs showed periosteal new bone formation around a metatarsal. (There was no finger clubbing.) A diagnosis of polyarteritis nodosa was proved by muscle biopsy. Despite two short courses of ACTH the patient died of rapidly progressing renal failure. Necropsy showed evidence of polyarteritis (mostly healed) in heart, spleen, voluntary muscle and skin. There was widespread destruction and fibrosis of renal glomeruli. Macroscopically the lungs showed only emphysema, but microscopically there were small granulomatous foci with necrotic centres; some of these may have been centred on damaged arteries.

A bronchitic illness is a less frequent type of presentation in polyarteritis nodosa than the pneumonic type. Sometimes the two may be combined.

The features which make a diagnosis of simple bronchitis unlikely are the evidence of a constitutional illness (loss of weight, lassitude, and a high E.S.R.), undue dyspnœa, and often also the presence of eosinophilia.

The significance of periosteal new bone formation in the absence of clubbing in this patient is not clear. Reference was made earlier (case 2) to the development of hypertrophic osteoarthropathy in association with pulmonary polyarteritis nodosa, and seven other patients with lung involvement in the Medical Research Council series were also noted to have finger clubbing. Hypertrophic osteoarthropathy has also been reported in a case of polyarteritis nodosa in the complete absence of any lung lesion (Lovell and Scott, 1956).

(iii) *The Asthmatic Type of Illness*

Case 5. A housewife aged 40 developed in November 1949 a persistent cough productive of 100-200 ml. of sputum daily, with frequent blood staining. The cough was associated with attacks of asthma, and also progressive breathlessness, lassitude, generalised aching of the body and limbs, and night sweats. She spent most of the next six years in bed, and during this time she lost 3½ stones (22 kg.) in weight. Serial chest X-rays were at first normal; but in 1951 there appeared a coarse miliary mottling throughout both lung fields (Fig. 2A, Plate XIII). Acid-fast bacilli were absent from the sputum throughout the illness, and the lung infiltrations cleared spontaneously. Although respiratory symptoms dominated the course of the illness, nevertheless there was from time to time evidence of lesions in other systems. From 1952 onwards she had periodic crops of painful subcutaneous nodules, and in 1956 she had four attacks of abdominal pain with diarrhœa and bloody stools. During the same year also she twice had macroscopic hæmaturia. However, despite several hospital admissions the true diagnosis was not uncovered, and she continued to lead a painful bedridden existence. Attacks of asthma persisted, and chest X-rays now showed gross emphysema of the left lung with much displacement of the mediastinum towards the right (Fig. 2B, Plate XIII).

On 25.9.56 she was admitted under the care of Mr. C. A. Jackson at St. Charles's Hospital. On examination she was emaciated and slightly febrile. Her fingers were clubbed, and there was reduced expansion of the left side of the chest with deviation of the trachea to the right. Other systems were essentially normal, and her blood pressure ranged from 130/80 to 150/100 mm. of mercury. The urine was normal, and two white blood counts (made postoperatively) showed neutrophilia only. At bronchoscopy the left lower lobe bronchus was seen to be stenosed, and it was presumed that emphysema was secondary to a valvular obstruction. On 11.10.56 the chest was opened through the bed of the left sixth rib, when it was found that the left hemithorax was almost completely filled by a giant cyst of the lower lobe. When this was ruptured it was seen that the upper lobe also contained many small cysts. The lower lobe was resected; because of its cystic state, the upper lobe could be inflated only enough to fill about half the pleural space. Microscopy of the resected lobe showed widespread polyarteritis of small and medium-sized arteries, the lung parenchyma itself being atrophic; fibrosis was remarkably slight.

Prednisone (10 mg. q.d.s.) was started on 31.10.56, and this was followed by rapid improvement in general well-being, abatement of fever, and a fall in the E.S.R. from 50 to 12 mm. in one hour. Recovery was interrupted by severe bronchitis, and later by infection of the pleural space. But thereafter she made

excellent progress and was discharged to convalescence, still receiving the same dose of prednisone. There has been no return of asthma since the start of steroid therapy.

Bronchial asthma is the most widely recognised presentation of polyarteritis nodosa with lung involvement (Rackemann and Greene, 1939; Harkavy, 1941; Wilson and Alexander, 1945; Churg and Strauss, 1951; Engfeldt and Zetterström, 1956; etc.). It occurred in twelve of the thirty-two cases with lung involvement in the Medical Research Council series. Most authors have regarded it as ordinary (allergic) asthma progressing to polyarteritis nodosa, but Rose and Spencer (1957) came to the conclusion from their study that it was a distinct entity, associated throughout its course with the presence of specific lung lesions. In patients with polyarteritis nodosa and asthma there is no family history of allergic disease; the onset is often later in life than in the case of allergic asthma; loss of weight may be considerable; high eosinophilia is general, and often exceeds 5,000/mm.^{3} (the above case was exceptional in this respect); chest X-rays frequently show transient infiltrations; and necropsy nearly always shows typical polyarteritic lung lesions of the same type as those seen in patients who had a pneumonic illness.

The interval between the onset of respiratory illness and the appearance of systemic polyarteritis tends to be longer in patients with asthma, and may sometimes be as much as seven years. The individual attacks resemble those seen in ordinary bronchial asthma, though they tend to be severe and resistant to treatment. Attacks usually recur at short intervals, but sometimes remissions may last as long as eighteen months.

Case 5 was of particular interest because of the development of a giant tension cyst—a manifestation of polyarteritis nodosa which has not been previously described. The disease quite often produces granulomatous lesions in the bronchial wall; but it is unusual for these to lead to destruction of the cartilage.

Case 6 (Case 70 in the Medical Research Council series). A 16-year-old boy developed a productive cough, followed in one month by asthmatic attacks of increasing frequency and severity. A year later he was admitted to hospital for the fourth time for treatment of the asthma. At this time he had persistent tachycardia and low-grade fever, and was producing about 300 ml. daily of thick foul-smelling blood-stained sputum. The nasal mucosa was pale and hypertrophic, with polyp formation. His urine contained a trace of protein, and he had a blood eosinophilia of 1,700/mm.^{3}. The lungs appeared normal on X-ray. He died suddenly seventeen months from the onset of the illness. At necropsy there was widespread granulomatous polyarteritis in the lungs, and small granulomata not related to arteries were found in the liver and kidney.

This patient illustrates the frequent severity of the asthmatic attacks in polyarteritis nodosa, and also the interesting finding of typical granulomata in the liver and kidneys during what appeared clinically to be a solely respiratory phase of the disease. Zuelzer and Apt (1949) reported three similar cases of asthma and eosinophilia in children in whom they were able to demonstrate eosinophilic granulomata by liver biopsy.

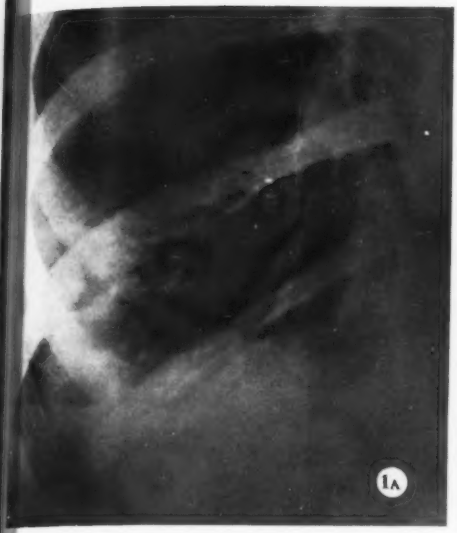

FIG. 1A.—*16.5.51*. Two abscesses with fluid levels in the right lower lobe, with surrounding pneumonia.

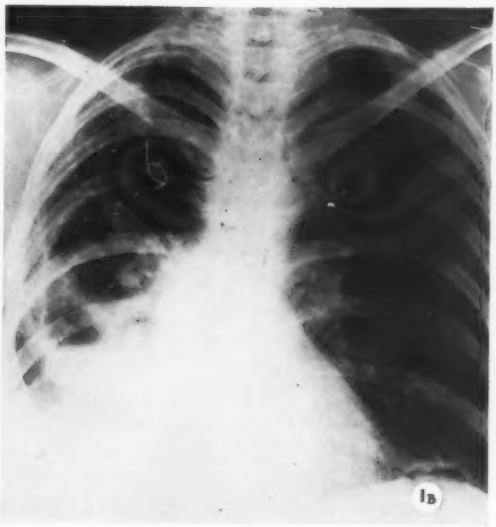

FIG. 1B.—*29.9.53*. Enormous multilocular abscess in the right lower lobe and a smaller one in the left lower lobe, developing during cortisone treatment. (The wire ligature remains from the previous lobectomy.)

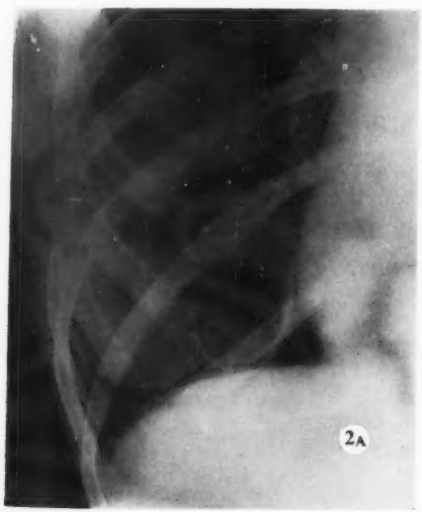

FIG. 2A.—Part of a generalised coarse miliary infiltration.

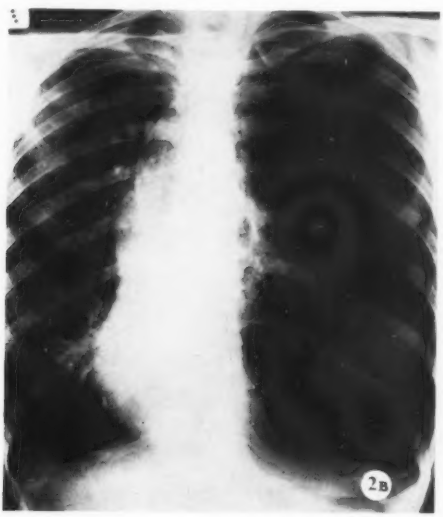

FIG. 2B.—(5 years later). A giant cyst has developed in the left lung, with much mediastinal displacement and extension of the cyst to the right of the mid-line.

To face p. 118

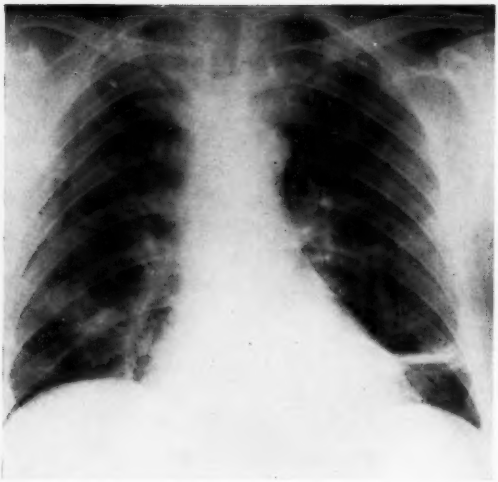

FIG. 3.—Irregular opacities of moderate density in the right lower zone. Horizontal linear opacity in the left lower zone, with a little adjacent low-density infiltration. General enlargement of the heart.

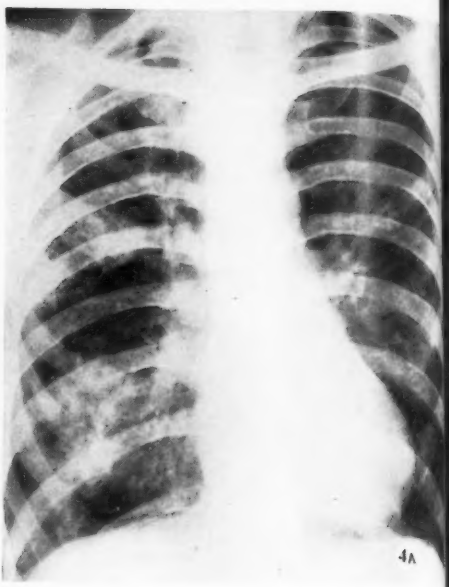

FIG. 4A.—*12.2.49.* Poorly defined rounded areas mottling in right lower and mid-zones.

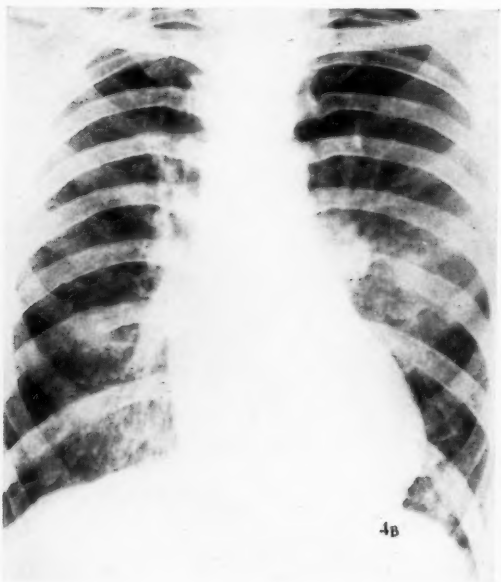

FIG. 4B.—*15.9.49.* Some resolution in the previous lesions, except for residual striations in the right cardio-phrenic angle, which are now denser. New infiltrations in the left lower and mid-zones. Increase in heart size.

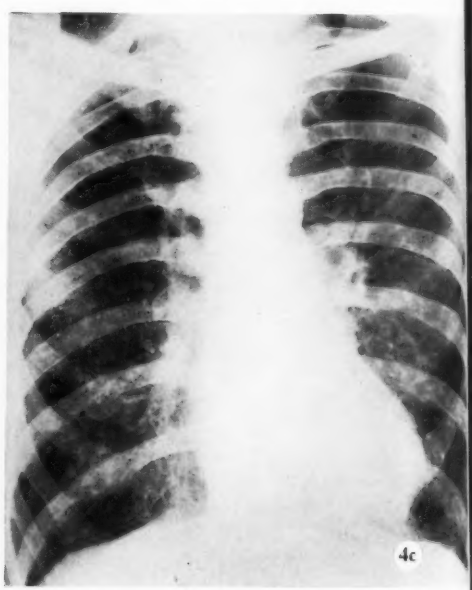

FIG. 4C.—*11.10.49.* Considerable resolution of all lesions except at the right cardio-phrenic angle. The heart has returned almost to its original size.

Radiological Appearances of the Lungs

Although nearly all cases of polyarteritis nodosa with lung involvement show radiological changes in the lungs at some stage of the disease, the appearances are extremely variable and not in any way specific to this condition. They seem to result mainly from the presence of necrotising and granulomatous lesions rather than from arteritis; for in the absence of such lesions the X-ray appearances may be entirely normal even when necropsy reveals extensive pulmonary polyarteritis.

The nearest approach to a characteristic radiological picture is the presence of numerous small shadows of miliary or near-miliary size (Fig. 2A, and also Crofton *et al.*, 1952; Ellman and Cudkowicz, 1954; Rose and Spencer, 1957). These may be confined to one lobe or spread throughout both lungs. They tend to be slightly larger and more irregular than the shadows of miliary tuberculosis.

In patients with an asthmatic or bronchitic type of illness transient infiltrations may occur without any associated change in the patient's symptoms or general condition. An example of this is shown in Fig. 3; these lesions later disappeared completely. This illustrates the need for repeated chest X-rays in suspected cases of pulmonary polyarteritis nodosa.

In patients with a pneumonic type of illness the lesions tend to be more extensive, denser and more persistent. They may be either irregular or rounded in shape. Their borders do not usually conform to lobar or segmental divisions, although smaller lesions may coalesce and come to occupy most of one lobe. Cavitation is not uncommon, and may occur in any part of the lung. The example described earlier in case 2 (Fig. 1A) is of interest because of the subsequent enormous enlargement of the cavity which occurred during cortisone treatment (Fig. 1B). A pleural effusion quite often develops over an area of pneumonia.

Pneumonic lesions may be progressive, but more often they resolve in one area only to appear in another. The rates of growth and resolution tend to be rather faster than in the case of tuberculosis, but are slower than in Loeffler's syndrome. Figs. 4A, B and C illustrate a typical sequence. In some cases healing appears radiologically to be complete; others show evidence of fibrosis. In either event necropsy usually shows extensive disorganisation and chronic lung damage. In one case in the Medical Research Council series healing was accompanied by calcification.

The Phase of Systemic Generalisation

In a small minority of cases evidence of pulmonary and systemic lesions appears simultaneously. Usually however the disease begins with a respiratory illness which is followed after a variable interval by deterioration in the patient's general condition and signs of polyarteritis in systemic organs. Thereafter the tempo of the disease is accelerated and (in the absence of cortisone therapy) death usually occurs within a few weeks or months. Exceptionally the systemic phase may be interrupted by a temporary remission.

The clinical manifestations of polyarteritis in systemic organs are in the main identical with those which occur in cases without lung involvement, and have already been fully described by, amongst others, Grant (1940), Miller and

Daley (1946), and Lovell and Rose (1955). Only two patterns need be mentioned here as being particularly characteristic of cases with lung involvement. The first is the occurrence of episodes of bloody diarrhœa, due to involvement of small mesenteric arteries. The second is the appearance of severe acute nephritis (Wegener, 1939; Davson *et al.*, 1948): the patient suddenly develops oliguria or anuria associated with rapidly progressive renal failure, macroscopic or heavy microscopic hæmaturia, and perhaps also œdema. By contrast with ordinary acute glomerulonephritis, the blood pressure does not tend to rise at this stage; but occasionally the patient survives this acute phase and enters a chronic phase of rising blood pressure and blood urea.

Diagnosis

A possible diagnosis of polyarteritis nodosa should be considered whenever a patient with atypical lung disease develops unexplained lesions in other organs, especially if there is also eosinophilia or asthma. It is most desirable in such cases to obtain pathological proof of the diagnosis before starting cortisone treatment; for if the latter is to be effective it may require prolonged and heavy dosage, productive of unpleasant and sometimes fatal side-effects. Deaths attributable to cortisone have been known to occur in patients treated on a mistaken clinical diagnosis of polyarteritis nodosa, when the real disease required quite different therapy. Fortunately it is possible in a majority of cases to obtain proof of the diagnosis by biopsy; but to be successful this may need to be repeated, and in view of the focal nature of the lesions it is important to cut serial sections of the whole of the available material.

The highest proportion of successes is achieved by biopsy of skin lesions. These must, however, be recent and non-ulcerated; for, on the one hand, healed arterial lesions may be unrecognisable, and on the other, ulceration and secondary infection make it impossible to determine whether vascular changes are primary or secondary. In the absence of suitable skin lesions, "blind" muscle biopsy probably offers about a 50 per cent. chance of a positive result; equivocal results are much less common than in the case of skin biopsy. The most suitable sites are probably the pectoral or calf regions; the volume of muscle removed must be sufficient to contain several small arteries.

If in a clinically probable case no success is achieved from two or three attempts at biopsy, it is often justifiable, despite the known risks, to proceed with steroid treatment; for in the absence of effective treatment the disease is nearly always fatal, and severe and irreversible damage to vital organs may appear without warning. The principles and a suggested scheme of therapy have been described by Lovell and Rose (1955).

Since the initial respiratory phase of polyarteritis nodosa with lung involvement may sometimes long precede the appearance of generalised disease, especially in patients with asthma, it is clear that there must be a number of such patients under medical care in whom the true diagnosis is at present quite unrecognised. The question is thus raised of whether these patients can be diagnosed before they develop widespread disease. The clinical and radiological pattern of the respiratory illness is admittedly variable; nevertheless it should sometimes be possible, at least in cases where high eosinophilia narrows the field of possible diagnoses, for the presence of polyarteritis nodosa to be

suspected. The experience of Zuelzer and Apt (1949) in such patients would seem to justify an attempt to demonstrate typical granulomata by liver biopsy, at least if that organ is clinically enlarged. Otherwise there is no means of proving the diagnosis at the time, although follow-up of the patients over a long period would be of great interest.

Differential Diagnosis

The principal lung diseases from which polyarteritis nodosa has to be distinguished are tuberculosis, sarcoidosis, cancer, bronchial asthma, parasitic infestations and simple chronic infections.

The commonest error in the interpretation of the lung lesions of polyarteritis nodosa is to diagnose tuberculosis. This mistake was made in cases 1 and 3 described earlier, and it has probably been made in a number of cases reported in the literature (Ferrari, 1903; Vance and Graham, 1931; Herrman, 1933; Wechsler and Bender, 1942, case 3; Jones, 1942, case 7; Banowitch *et al.*, 1942, case 5; and Contratto, 1947, case 1). Both diseases may present with loss of weight, fever, productive cough, high E.S.R. and similar radiological changes. In the case of polyarteritis nodosa the distinctive features of the respiratory illness are the complete absence of tubercle bacilli from the sputum (even in the presence of cavitation), an E.S.R. that is often a good deal higher than in tuberculous disease of similar extent, the frequent presence of eosinophilia, and a tendency for lesions to heal radiologically rather more rapidly than in tuberculosis. In addition of course there is often evidence of disease in other systems.

Sarcoidosis, like polyarteritis nodosa, may produce pulmonary disease associated with a raised E.S.R., high plasma globulin, and evidence of lesions in other organs. Confusion has sometimes also arisen histologically between the granulomatous lesions of the two conditions. In polyarteritis nodosa, however, there is no tendency for tuberculin sensitivity to be lost, nor for the salivary glands to enlarge; lymphadenopathy is a relatively uncommon feature, and in particular does not involve the hilar lymph nodes. The clinical manifestations of many of the visceral lesions of polyarteritis nodosa, such as those in the heart or kidney, are not reproducible by sarcoidosis.

In three cases in the Medical Research Council series the chest X-ray appearances were mistakenly attributed to malignant metastases, until they unexpectedly resolved. The cachectic state of many patients with polyarteritis nodosa makes such a mistake easy.

The distinction from ordinary (allergic) bronchial asthma has been described already in the discussion of case 5; the two conditions appear to be quite distinct.

The radiological changes and eosinophilia produced by pulmonary ascariasis (Loeffler's syndrome) may be distinguished by their tendency to occur in the summer, by the absence of any severe general illness, and by the rapid and complete resolution of the lesions. Tropical eosinophilia is recognisable by its response to neoarsphenamine bromide.

The association in polyarteritis nodosa of high blood eosinophilia with muscle pains and respiratory (and perhaps also gastro-intestinal) symptoms may suggest the possibility of trichiniasis. But usually the severity of the constitu-

tional illness and the evidence of involvement of other organs (such as the kidneys or peripheral nerves) suggests the true diagnosis.

One of the most difficult clinical decisions may be whether to attribute a respiratory history preceding the onset of generalised polyarteritis nodosa to specific lung lesions or to non-specific chronic infections. Rose and Spencer (1957) found evidence of long-standing respiratory infection preceding the onset of the disease in 25 per cent. of the whole series and also in 25 per cent. of cases with specific lung involvement. The infections were commonly due to chronic bronchitis or bronchiectasis; they showed no unusual feature either clinically, radiologically or pathologically. By contrast with specific polyarteritic lung disease, these non-specific infections often dated back to childhood; they were not progressive; there was no evidence of an unexplained constitutional illness; and they did not tend to be associated with eosinophilia, nasal granuloma, or atypical lung infiltrations.

Summary

From a study of a series of 111 proven cases of polyarteritis nodosa undertaken on behalf of the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council, it appeared that lung involvement occurred in about one-third. The respiratory illness in these patients generally preceded evidence of polyarteritis in other organs, and took the form of pneumonia, bronchitis or asthma. Radiologically the appearances of the lesions were varied, and no specific patterns could be recognised. The problems of the diagnosis of this syndrome and of its distinction from other conditions are discussed.

I am grateful to the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council for permission to make use of data collected while I was employed on their behalf. I also wish to thank the physicians and surgeons at the various hospitals visited for permission to quote the histories of patients who were under their care.

REFERENCES

BANOWITCH, M. M., POLAYES, S. H., and CHARET, R. (1942): *Ann. intern. Med.*, **16,** 1149.
CHURG, J., and STRAUSS, L. (1951): *Amer. J. Path.*, **27,** 277.
CONTRATTO, A. W. (1947): *Arch. intern. Med.*, **80,** 567.
CROFTON, J. W., LIVINGSTONE, J. L., OSWALD, N. C., and ROBERTS, A. T. M. (1952): *Thorax*, **7,** 1.
DAVSON, J., BALL, J., and PLATT, R. (1948): *Quart. J. Med.*, **17,** 175.
ELLMAN, P., and CUDKOWICZ, L. (1954): *Thorax*, **9,** 46.
ENGFELDT, B., and ZETTERSTRÖM, R. (1956): *Acta. med. scand.*, **153,** 337.
FERRARI (1903): *Beitr. path. Anat.*, **34,** 350.
GODMAN, G. C., and CHURG, J. (1954): *Arch. Path.*, **58,** 533.
GRANT, R. T. (1940): *Clin. Sci.*, **4,** 245.
HARKAVY, J. (1941): *Arch. intern. Med.*, **67,** 709.
HERRMAN, W. G. (1933): *Amer. J. Roentgenol.*, **29,** 607.
JONES, G. M. (1942): *Ann. intern. Med.*, **16,** 920.
KUSSMAUL, A., and MAIER, R. (1866): *Dtsch. Arch. klin. Med.*, **1,** 484.
LOVELL, R. R. H., and SCOTT, G. B. D. (1956): *Ann. rheum. Dis.*, **15,** 46.
LOVELL, R. R. H., and ROSE, G. A. (1955): *Postgrad. med. J.*, **31,** 382.
MILLER, H. J., and DALEY, R. (1946): *Quart. J. Med.*, **15,** 255.
RACKEMANN, F. M., and GREENE, J. E. (1939): *Trans. Ass. Amer. Phy.*, **54,** 112.
ROSE, G. A., and SPENCER, H. (1957): *Quart. J. Med.*, **50,** 43.
VANCE, B. M., and GRAHAM, J. E. (1931): *Arch. Path.*, **12,** 521.
WALTON, E. W., and LEGGAT, P. O. (1956): *J. clin. Path.*, **9,** 31.
WECHSLER, I. S., and BENDER, M. B. (1942): *J. Mt. Sinai Hosp.*, **8,** 1071.
WEGENER, F. (1939): *Beitr. path. Anat.*, **102,** 36.
WILSON, K. S., and ALEXANDER, H. L. (1945): *J. Lab. clin. Med.*, **30,** 195.
ZUELZER, W. W., and APT, L. (1949): *Amer. J. Dis. Child.*, **78,** 153.

PULMONARY LESIONS IN POLYARTERITIS NODOSA

By H. Spencer

From the Department of Pathology, St. Thomas's Hospital Medical School, London, S.E.1

Until fifty years ago polyarteritis nodosa was infrequently recognised and was considered to be a rare disorder. During the past three decades many series of cases and individual case reports have appeared and interest now largely centres upon consideration of the ætiological factors involved in its production, together with the study of the relationship of polyarteritis nodosa to other changes which sometimes coexist with the arterial disorder. The experimental hypersensitivity angeitis described by Rich and Gregory (1943), the existence of polyarteritic lesions in some cases of experimentally induced malignant hypertension, and the recent classification of the disease suggested by Zeek (1952) have raised doubts as to whether polyarteritis nodosa is a single disease entity or the end-product of several differing processes acting upon arteries.

Although in classical polyarteritis nodosa the pulmonary vessels may be involved, it has been noticed that these are often spared whilst the bronchial arteries are affected as frequently as other systemic arteries. Gruber (1926) stated that the bronchial arteries were involved in 8 per cent. of cases, whereas the pulmonary arteries were implicated in only 3·7 per cent.

During a recent survey of 111 cases of polyarteritis nodosa conducted under the auspices of the Medical Research Council (Rose and Spencer, 1957), an opportunity occurred to study both the clinical histories and histological material from many cases. It was found that some were associated with peculiar granulomatous and necrotising lesions in various organs, including the lungs, and that these cases showed a high incidence of polyarteritis nodosa affecting the pulmonary arteries. Involvement of the pulmonary arteries was usually associated with a generalised blood and local tissue eosinophilia. The relationship of the granulomatous lesions to the underlying polyarteritis nodosa has not always been appreciated and the lesions have received a variety of names, including eosinophilic granulomata, Löffler's syndrome, Wegener's granulomatosis, and rheumatic and para-rheumatic disorders.

This paper includes two examples of unusual necrotic and granulomatous lesions in the lung and three further cases with polyarteritic changes confined to the pulmonary circulation and associated with pulmonary hypertension. All five cases were examined by the writer and three were included in the Survey mentioned above. For reasons that will be stated, the last three cases are referred to as pulmonary polyarteritis associated with pulmonary hypertension, and not as pulmonary polyarteritis nodosa.

Case Reports

Case 1. A man aged 44 who was admitted to hospital with a history of seven weeks' pain in the left leg, followed by a continuous fever and blindness

(*Received for publication August* 1, 1956.)

in the left eye for one week. He had previously been a healthy man. Ten days after the onset of his illness he complained of bilateral pain in the front and axillary part of the chest. Shortly after this he produced some rusty sputum and developed a sore mouth and throat. An X-ray a fortnight after the onset of the illness showed a homogeneous opacity in the left apical region and two further rounded opacities in the left lower zone. His sputum remained rusty and he was treated with penicillin. An X-ray of the chest on the twenty-eighth day of the illness showed little change from the previous one. On the fortieth day a large sloughing ulcer appeared on the tongue and the patient also had considerable albuminuria and slight hæmaturia. On the forty-seventh day of the illness, on admission to hospital, there was a widespread non-irritating acneform rash of the skin, ulceration of the tongue, mouth and throat, a left pleural effusion and a palpable liver. The fundus of the left eye showed several small hæmorrhages near to and one large one overlapping the disc. There was only faint perception of light. The left biceps jerk was reduced. There was a naked-eye degree of hæmaturia and a blood urea of 484 mg. per cent. The left pleural effusion was tapped and the fluid contained much blood and many pus cells, but the culture was sterile. He died on the fiftieth day after the commencement of his illness.

Post-mortem examination showed many red macules in the skin over the shoulders, chest and legs. In the lungs were diffuse patches of hæmorrhage and bronchopneumonia, pale creamy-white areas of consolidated tissue in the region of the left apex up to 3 cm. in diameter, and a left fibrinous pleurisy with a small effusion. Numerous infarcts were found in the renal cortex, pale areas related to vessels in the spleen, and an infarct in the left testis.

Microscopical examination confirmed the presence of changes due to acute polyarteritis nodosa in the lungs, kidneys, heart, spleen and peri-adrenal arteries. A more detailed account of the lung lesions is given below.

Case 2. A man aged 47 who had complained of " bronchitis " for eleven years. Nine years before death he had left pleurisy and seven years later a right pleural effusion of unknown ætiology. Bronchoscopic examination was negative. One year before death he was found to have an opacity in the middle zone of the right lung. Four weeks before admission he had had sharp left-sided chest pain which lasted a minute but did not recur. On admission his temperature was 103° and he was cyanosed. There was a poor air entry and deficient movement over the upper part of the right lung, and a fine pleural rub was present in the right anterior axillary line. X-ray showed right upper lobe consolidation and cavitation. Penicillin, aureomycin, streptomycin and terramycin were all tried in turn without beneficial effect. A few days before death he developed bullous hæmorrhagic spots on the lips, face and ears, a very sore throat, and hæmaturia. Repeated direct examination and cultures of sputum all failed to show the presence of acid-fast bacilli.

Post-mortem examination showed numerous reddish raised skin lesions, some ulcerated, situated mainly around the lips, external ears and right forearm. The lesions had started as vesicles into which hæmorrhage occurred followed by ulceration. There was very extensive ulceration of the surface of the tongue, fauces, tonsils, pharynx, ary-epiglottic folds, larynx, trachea and main bronchi. Almost the entire upper lobe of the right lung, with the exception of a small zone near the apex, was solid and replaced by mottled creamy-white and black tissue which felt firm and macroscopically resembled an area of unresolved pneumonia. In the centre of the affected lobe there were irregular

PLATE XV

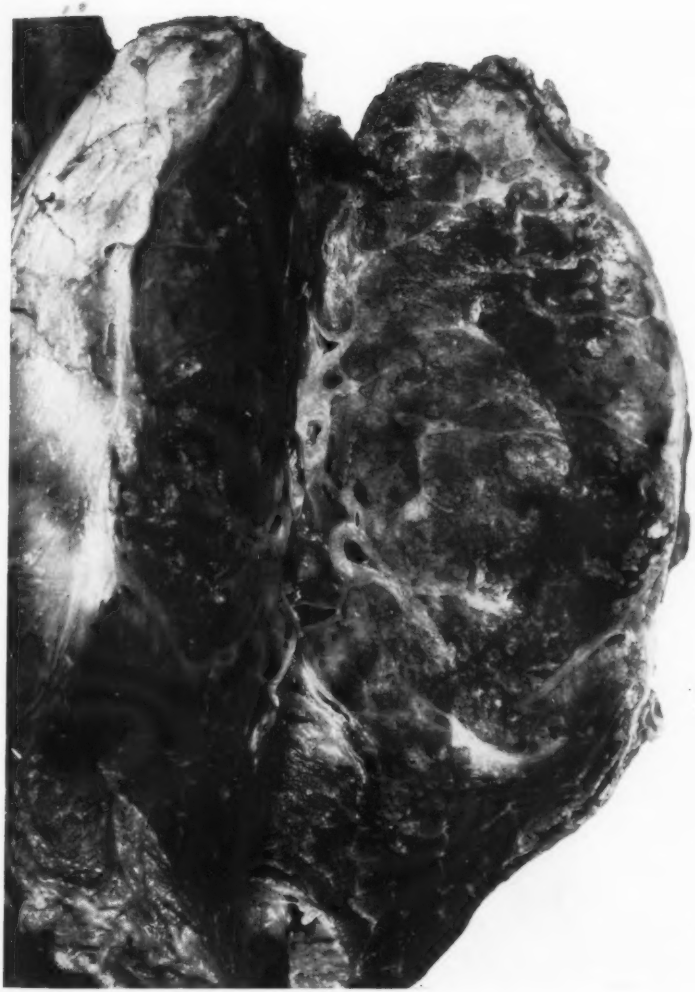

FIG. 1.—The upper lobe of the right lung from Case 2 showing the cut surface. This lobe was airless, indurated and contained a ragged cavity which can be seen beneath the pleural surface. The pleura was covered with a dense layer of fibrous tissue.

To face p. 124

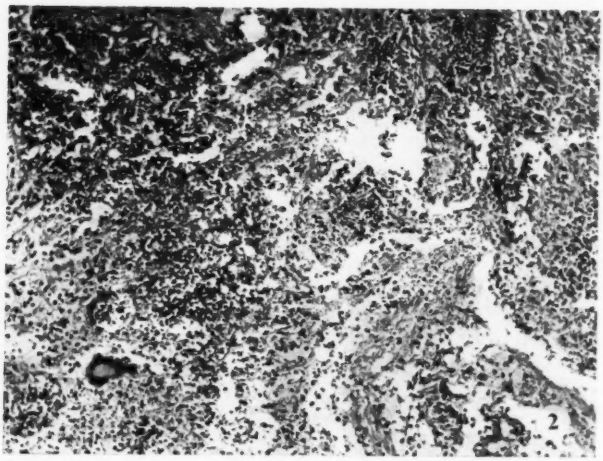

FIG. 2.—Section from the edge of necrotic lung in Case 2 showing acute and chronic inflammatory cell infiltration and a giant cell.
(×140)

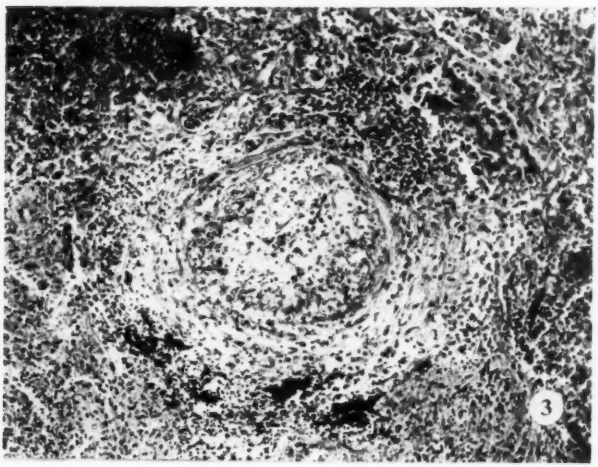

FIG. 3.—Section showing a vessel outside the infarcted area (Case 2) surrounded by acute and chronic inflammatory cells and also displaying considerable intimal reaction consisting of connective tissue heavily infiltrated with inflammatory cells.
(×140)

cavities resembling abscesses (Fig. 1). The pleural surface over the entire right lung was adherent to the chest wall and the adhesions were most dense over the upper lobe. The middle and lower lobes of the right lung were normally aerated. In the upper lobe of the left lung there were two irregular zones of consolidated tissue resembling those in the upper lobe of the right side, but no cavities were present. The left upper lobe was adherent to the chest wall and the remainder of the pleural sac contained yellowish fluid.

There was extensive superficial ulceration of the stomach involving the pyloric antrum and pylorus and extending into the first and second parts of the duodenum. The remaining mucous membrane in the ulcerated area was readily stripped off. The rest of the bowel was unaffected. The spleen was enlarged to approximately four times its normal size and its surface was covered with a film of fibrin beneath which were seen pale, irregular, greyish-white areas of infarction. Most of the organ was infarcted, but in the few non-infarcted zones small vessels could be seen surrounded by a narrow mantle of greyish-red splenic tissue.

The kidneys were both enlarged, and on stripping the capsules there were many creamy-white areas in the underlying cortex which was thickened and greatly swollen. The remaining organs showed only changes compatible with acute heart failure.

Cultures were made of the contents of the right upper lobe and of the spleen, but these proved to be sterile on both aerobic and anaerobic culture. No fungi could be identified or grown.

Owing to the similarity in the microscopical appearance of the lung lesions in cases 1 and 2 a single description will suffice for both. Numerous sections were taken from the upper lobe of case 2 and from the necrotic greyish-white areas in the upper lobe of case 1. All sections were stained with hæmatoxylin and eosin, Van Gieson's stain, and also stained for acid-fast bacilli by both Ziehl-Neelsen and the auramine fluorescent method.

The lungs showed extensive areas of complete destruction in which the nuclei of the cells were undergoing karyorrhexis and were mixed with fibrinous exudate. It was also possible in many places to make out the ghost outlines of the dead lung tissue, and in this respect the lesions resembled infarcts. They failed, however, to show the normal shape and distribution of infarcts resulting from occlusion of branches of the pulmonary arteries. The edge of the infarcted tissue was surrounded by many foreign body and Langhans type of giant cells, moderate numbers of lymphocytes, plasma cells, a few histiocytes, and large numbers of polymorph leucocytes and proliferating fibroblasts (Fig. 2). There were very few eosinophils.

In places the fibroblasts tended to pallisade radially around the necrotic zones. Outside these zones and in places extending to their edges, there was much non-specific interstitial fibrosis. The necrosis involved vessels and air passages by direct extension, where these lay in its path. No acid-fast bacilli were seen and no evidence that the lesions were tuberculous was ever found.

Outside the necrotic granulomatous lesions many medium-sized branches of the pulmonary arteries and veins showed an acute vasculitis characterised by considerable intimal proliferation of loose connective tissue, and a generalised infiltration of the whole vessel wall with polymorph leucocytes (Fig. 3). In many vessels, mainly arteries, there was complete or partial fibrinoid change in the media which in some instances was totally destroyed. In arteries undergoing repair occasional small giant cells were present. In case 2 in the un-

affected part of the lungs there were granulomatous polyarteritic lesions accompanied by eosinophil collections in the peri-adventitial tissues.

In addition to the above changes in the arteries and veins there were focal patches of alveolar capillary wall necrosis in the remaining normal and fibrosed parts of the lung. These patches were characterised by fibrinoid change of the capillary wall, nuclear karyorrhexis, outpouring of fibrinous exudate and an accumulation of polymorph leucocytes in the vicinity of the damaged capillary. The lesions were minute replicas of the changes observed in the large necrotic granulomatous areas and appeared to represent the initial lesion.

The kidneys in both cases showed necrotising glomerulitis accompanied by changes typical of acute polyarteritis nodosa in the arcuate and smaller arteries, and accompanied by infarcts in case 1. A detailed description of the renal lesions has not been included.

In case 2 the spleen was largely destroyed by infarcts which were of unusual distribution and in some places spared the vessels, which showed changes of an acute vasculitis similar to those described in the lung.

In both cases changes of acute polyarteritis nodosa were confirmed in other sites which included branches of the coronary, testicular and the peri-adrenal arteries.

Sections were taken from the skin, tongue, tonsil, trachea and stomach of case 2 and in each instance the surface epithelium was extensively ulcerated with considerable polymorph infiltration in the underlying tissue and fibrinoid change in the walls of the vessels below the floor of the ulcers. In sections where the surface epithelium was still intact the deeper arterioles showed mural fibrinoid changes with polymorph leucocyte and some eosinophil infiltration. There were also patches of " fibrinoid " change in undamaged collagenous fibrous tissue.

Case 3. A man aged 70 who had complained of " bronchitis " for the past forty years which became worse each winter. Four months before admission his symptoms became more pronounced. On admission to hospital he was dyspnœic and very cyanosed. He showed evidence of congestive heart failure and signs compatible with chronic bronchitis and emphysema. He died within two weeks of admission of congestive heart failure.

Post-mortem examination showed very great hypertrophy of the right ventricle and a very extensive healed infarct in the lower half of the anterior wall of the left ventricle. The lungs were moderately emphysematous but showed no evidence of bronchopneumonia or acute bronchitis. Death was attributed mainly to failure of the left ventricle, due to the chronic myocardial infarct.

Microscopical examination of the left ventricle confirmed the presence of an extensive healed infarct of the myocardium. The lungs showed minimal emphysematous changes masked by widespread collapse. Changes due to chronic bronchitis were present and all the larger branches of the pulmonary artery showed very extensive medial hypertrophy, intimal fibrosis and some fibrinoid changes in their walls confined mainly to the intima (Fig. 4). The smallest branches showed generalised fibrinoid change and polymorph infiltration of their walls (Fig. 5). This change was also observed to a slight extent in the pulmonary veins. The arteriolar changes were consistent with acute polyarteritis. No other organ showed any evidence of polyarteritis.

Case 4. A woman aged 21 who had had chronic mitral stenosis for many years but had recently developed lobar pneumonia from which she died.

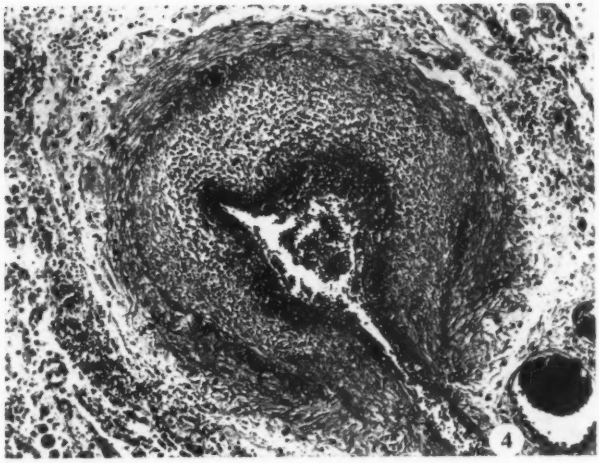

FIG. 4.—Section showing a medium-sized branch of the pulmonary artery from Case 3 in which the polyarteritic changes are almost entirely confined to the intima. There is also marked medial hypertrophy in this vessel.

(×140)

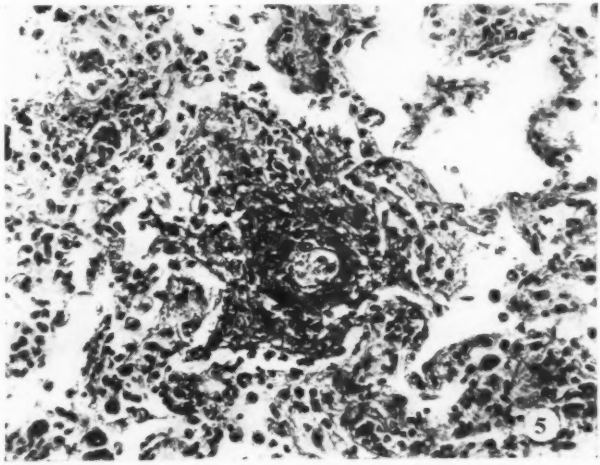

FIG. 5.—Section showing a small branch of the pulmonary artery (Case 3) about to divide into alveolar capillaries. Fibrinoid change is affecting the entire wall and there is accompanying inflammatory cell infiltration.

(×240)

To face p. 126

PLATE XVIII

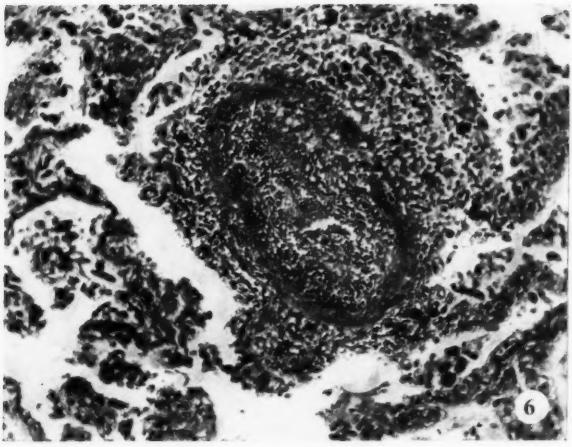

FIG. 6.—(Case 5). A branch of a pulmonary artery showing acute polyarteritic changes in a hypertrophied artery.

(×140)

At *post-mortem examination* a greatly hypertrophied right ventricle was found secondary to severe mitral stenosis. A few small hæmorrhages were found in the red consolidated lower lobe of the right lung. Both lungs showed chronic induration in addition to the recent pneumonic changes.

Microscopical examination: Many sections were made and in the smaller branches of the pulmonary arteries changes due to polyarteritis were present in addition to the lobar pneumonia and pulmonary infarction.

Case 5. A man aged 53 was first admitted to hospital four years before death with bilateral pleural effusions and a small pericardial effusion due to rheumatic heart disease. He was found to have mitral stenosis. During the next three years cardiac failure gradually increased in severity, eventually necessitating a mitral valvotomy. Following the operation his general condition improved but relapsed gradually a year later. He underwent a second operation for mitral valvotomy three weeks before death. After operation the jugular venous pressure remained raised and the patient developed a right hemiplegia. During the following three weeks heart failure increased and the patient died. Two years before death cardiac catheterisation had shown a pulmonary artery pressure of 81/39 mm. Hg. The clinical evidence suggested that it was probably higher shortly before death.

Post-mortem examination showed a very hypertrophied right ventricle and auricle, and an enlarged left auricle due to very severe mitral stenosis with complete calcification of both cusps. The pulmonary artery and its branches were macroscopically greatly thickened and showed a degree of atheromatous change normally only seen in a systemic artery such as the aorta. There was a large organising ante-mortem thrombus attached to the wall of the right pulmonary artery.

Microscopical examination: Section of the lung showed generalised hypertrophy of the walls of all the branches of the pulmonary artery and changes due to chronic heart failure. In addition many of the smaller branches of the pulmonary artery showed changes of acute polyarteritis (Fig. 6).

Discussion

In 1908 Dickson described a case of generalised polyarteritis nodosa with chronic necrotising interstitial pneumonia accompanied by giant cells in which no tubercle bacilli were discovered in the pulmonary lesions. Reviewing the literature, he discovered a similar case described by Ferrari (1903) which had been regarded as pulmonary phthisis in association with generalised polyarteritis but in which no acid-fast bacilli had been discovered. Mönckeberg (1905) reported a further case of pulmonary polyarteritis nodosa with focal areas of eosinophilic pneumonia and a granulomatous type of polyarteritis in other organs.

It was Wegener (1936, 1939) who drew attention to the frequent association of chronic granulomatous lesions in the upper air passages accompanied by focal necrotising pan-vasculitis in the lungs. Often the condition was accompanied by a renal disorder characterised by an acute embolic glomerulonephritis which led to death from renal failure in a few weeks.

More recently Godman and Churg (1954) described a further 6 cases all of which complained initially of symptoms referable to sinusitis or to an accompanying distinctive form of necrotising glomerulitis that caused the death of the patients from renal failure after a few weeks. They have attached the eponymous name of Wegener's granulomatosis to this condition.

During the course of the Survey (Rose and Spencer), 15 cases were found showing similar lung lesions to those described above, ranging mostly in size from 0·1 to 4 cm. On the radiological appearances 5 of these cases had been interpreted as tuberculous. Unlike cases 1 and 2, not all the remaining cases were associated with necrotising glomerulo-nephritis, though in several the larynx and trachea were extensively ulcerated.

Both cases 1 and 2 were accompanied by an acute embolic and necrotising type of glomerulo-nephritis, though this kind of renal lesion is not entirely confined to cases of polyarteritis nodosa involving the pulmonary vessels but may infrequently accompany the classical type of systemic polyarteritis. Godman and Churg considered that the necrotic and granulomatous lesions in the lungs were unrelated to the vasculitis, as they often found there was no relation between damaged vessels and these lesions. They considered that they originated as extravascular foci of collagen necrosis which spread subsequently to involve vessels. The present cases, however, appeared to start as an alveolar capillaritis which eventually involved both arteries and veins. As the capillaritis developed, fibrinous exudate collected in the alveoli accompanied by both acute and chronic inflammatory cells. Later the affected areas of the lung might either necrose or become organised.

In both the cases described above acute terminal ulceration of the oropharynx and major respiratory passages was present and this was considered an integral feature of the condition by Wegener and by Godman and Churg. In neither case 1 or 2 was a chronic granuloma found in the nose or accessory sinuses, although such granulomata are only found in cases of polyarteritis nodosa involving the pulmonary vasculature (Lindsay, Aggeler and Lucia, 1944; Godman and Churg, 1954).

No ætiological factor has so far been found and the numerous and repeated attempts to incriminate the tubercle bacillus have always proved negative. Furthermore, the rapidity with which the radiological lesions appear, change in character, and disappear, differentiate them from pulmonary tuberculosis. The X-ray appearances in this condition have been described by Kornblum and Fienberg (1955). The histological appearances, though superficially resembling both fulminating bronchopneumonic tuberculosis and infarcts, fail to show properly developed tubercles, and, despite the widespread and acute nature of the pulmonary lesions, never show a miliary dissemination.

In neither of the present 2 cases nor in other similar pulmonary lesions seen by Rose and Spencer in their recent survey was any evidence discovered of parasitic infestation of the lung. Although ascariasis is now considered responsible for Löffler's syndrome (Maier, 1943), the transient nature of this syndrome and the failure of others to demonstrate parasites in the lesions under discussion makes this ætiological cause unlikely. The close association with polyarteritis nodosa which has been recognised since the earliest description of these lesions indicates a common ætiology. The possibility that the changes represented a hypersensitivity state induced by drug therapy could not be excluded in case 2 but was improbable in case 1.

Cases 3, 4 and 5 are three further examples of a polyarteritic type of change confined to the pulmonary vasculature related to pulmonary hypertension caused by chronic bronchitis and emphysema and by mitral stenosis. Many

examples of the change have now been recorded since Old and Russell (1950) described the vascular changes in a case of Eisenmenger's type of congenital heart disease. Spencer (1950), Kipkie and Johnson (1951), Symmers (1952), McKeown (1952), Hicks (1953), Lopes de Faria (1954) and Braunstein (1955) have all described further cases in patients with either mitral stenosis, multiple pulmonary emboli, idiopathic pulmonary hypertension, congenital heart disease or pulmonary bilharziasis. In every case hypertension in the pulmonary circulation has been present.

Bayliss (1902) and more recently Byrom (1954) have both shown that high intra-arterial pressures lead to vasoconstriction of an artery. This change if long maintained leads to structural changes in the arterial walls as seen in essential and malignant hypertension, and if very severe, to acute necrotising polyarteritis. Further evidence to support the view that prolonged vasoconstriction is the important ætiological factor in the causation of this condition has been given by Scully and Hughes (1956), who showed that systemic arteries that had undergone vasoconstriction due to traumatic wounding sometimes showed acute necrotising polyarteritis in their smaller branches. The arterial lesions also closely resemble those found in animals with rapidly induced hypertension (Smith *et al.*, 1944) and in malignant hypertension in man. The necrosis of the arterial walls and fibrinoid change are sometimes accompanied by little or no cellular reaction and may thus be differentiated from polyarteritis nodosa, in which the inflammatory changes usually spread through and beyond the vessel wall into the surrounding peri-adventitial tissues. Because of these distinctive histological appearances and its special ætiological features it has been referred to in this paper as pulmonary hypertensive polyarteritis.

The five cases presented above illustrate how varied may be the pulmonary changes in polyarteritis nodosa and strongly support the theory of a varied ætiology. Although uncommon, the accompanying necrotic and granulomatous lesions (eponymously referred to as Wegener's granulomatosis) may give rise to considerable difficulty in clinical and radiological diagnosis. A condition showing the association of hæmaturia and rapidly increasing renal failure with a history of chronic nasopharyngeal granulomata and recent pharyngeal oral and tracheal ulceration, together with bizarre shadowing in the lung X-rays, should arouse suspicion of polyarteritis nodosa with lung involvement. In such a case confirmation should be sought by muscle biopsy.

However, in cases known to have pulmonary hypertension, no way has yet been devised of recognising ante-mortem whether polyarteritic changes exist, and the diagnosis of this type of change is at present based entirely on post-mortem findings.

Summary

Two cases of an unusual pulmonary granulomatous lesion associated with polyarteritis nodosa are described. This type of pulmonary lesion may give rise to considerable difficulty in X-ray and clinical diagnosis. It is frequently associated with rapid onset of renal failure due to acute glomerulo-nephritis and is accompanied by oro-pharyngeal and respiratory tract ulceration. The lesions appear to result from a pan-vasculitis rather than from extra-vascular collagen degeneration.

A further 3 cases are described of polyarteritis associated with pulmonary hypertension.

These cases add further evidence to the view that polyarteritis nodosa is a disease of varied ætiology.

REFERENCES

Bayliss, W. M. (1902): *J. Physiol.*, **28,** 220.
Braunstein, H. (1955): *Amer. J. Path.*, **31,** 837.
Byrom, F. B. (1954): *Lancet*, **ii,** 201.
Dickson, W. E. C. (1908): *J. Path. Bact.*, **12,** 31.
Ferrari (1903): *Beitr. path. Anat.*, **34,** 350. (Quoted by Dickson, 1908.)
Godman, G. C., and Churg, J. (1954): *Arch. Path.*, **58,** 533.
Gruber, G. B. (1926): *Zentralbl. f. Herz- u. Gefässkr.*, **18,** 145 *et seq.*
Hicks, J. D. (1953): *J. Path. Bact.*, **65,** 333.
Kipkie, G. F., and Johnson, D. S. (1951): *Arch. Path.*, **51,** 387.
Kornblum, D., and Fienberg, R. (1955): *Amer. J. Roentgenol.*, **74,** 587.
Lindsay, S., Aggeler, P. M., and Lucia, S. P. (1944): *Amer. J. Path.*, **20,** 1057.
Lopes de Faria, J. (1954): *J. Path. Bact.*, **68,** 589.
Maier, C. (1943): *Helvet. Med. Acta*, **10,** 95.
Mönckeberg, J. G. (1905): *Dtsch. med. Wschr.*, **31,** 975.
McKeown, F. (1952): *Brit. Heart J.*, **14,** 25.
Old, J. W., and Russell, W. O. (1950): *Amer. J. Path.*, **26,** 789.
Rich, A. R., and Gregory, J. E. (1943): *Bull. Johns Hopkins Hosp.*, **72,** 65.
Rose, G. A., and Spencer, H.: *Quart. J. Med.*, 50, 43.
Scully, R. E., and Hughes, C. W. (1956): *Amer. J. Path.*, **32,** 805.
Smith, C. C., Zeek, Pearl M., and McGuire, J. (1944): *Amer. J. Path.*, **20,** 721.
Spencer, H. (1950): *J. Path. Bact.*, **62,** 75.
Symmers, W. St.C. (1952): *J. clin. Path.*, **5,** 36.
Wegener, F. (1936): *Verhandl. deutsch. path. Gesellsch.*, **29,** 202-9.
(1939): *Beitr. path. Anat.*, **102,** 36-68.
Zeek, Pearl M. (1952): *Amer. J. clin. Path.*, **22,** 777.

PULMONARY EOSINOPHILIA

REPORT OF A CASE

By C. S. Hunter

From the Manchester team of Medical Research Council's Tuberculosis Vaccines Trial

According to Crofton *et al.* (1952), pulmonary eosinophilia covers a wide range of diseases, which however form a continuum, both clinically and pathologically. They suggested the following classification (pointing out that the sub-groups fade into one another): (i) simple pulmonary eosinophilia or Loeffler's syndrome (transient infiltrations); (ii) prolonged pulmonary eosinophilia (prolonged or recurrent infiltrations without asthma); (iii) pulmonary eosinophilia with asthma (infiltrations with asthma); (iv) tropical pulmonary eosinophilia (usually with asthmatic symptoms); (v) polyarteritis nodosa.

With regard to the last sub-group, Rose and Spencer (1957), referring to these cases as "eosinophilic polyarteritis," have shown that pulmonary cases may precede systemic polyarteritis nodosa by periods varying from one to seven years. The literature of polyarteritis nodosa and lung changes has been reviewed by Ellman and Cudkowicz (1954).

The following case illustrates both (i) and (ii) above; it is also of interest in that the patient had asthma up to the age of 16 while none of Crofton's patients in these sub-groups had any associated asthma.

The patient was a 21-year-old male, recently demobilised after completion of his National Service. He was symptomless. Up to the age of 16 he had suffered from mild asthma, and he had had pneumonia twice in the past. Three years previously he had had a Mantoux test which had been positive.

Following a routine miniature chest X-ray, he was recalled by the Mass Radiography Unit, and a large plate (Fig. 1) was taken on May 14, 1956. This showed an opacity in the right mid-zone, and infiltration in the left upper zone strongly suggestive of active pulmonary tuberculosis.

He was seen at the Redhill Chest Clinic on May 22, 1956, and the film taken on that day (Fig. 2) showed that the opacity in the right mid-zone had unexpectedly cleared completely. A white blood count was then performed and showed a total count of 11,600, of which 1,200 were eosinophils. The sedimentation rate was normal. Mantoux test was positive to 1/1,000 O.T.

At this stage the miniature X-ray taken prior to National Service was located and rechecked; it was still considered normal.

He was seen again at the clinic on June 5, 1956. The film taken that day (Fig. 3) showed persistence of the left upper zone opacities, and was in fact practically identical with Fig. 2. In view of the appearance of these opacities, and their persistence, a double diagnosis of pulmonary eosinophilia and active pulmonary tuberculosis was made, and he was admitted to Milford Chest

(*Received for publication January* 31, 1957.)

Hospital on June 18, 1956. The double diagnosis was accepted and treatment with anti-tuberculous chemotherapy was started. Mantoux 1/1,000 O.T. was repeated and was strongly positive. The appearance of the lesion on tomograms was typical of active pulmonary tuberculosis without cavity.

Neither at the clinic nor in hospital were tubercle bacilli recovered.

His progress in hospital was satisfactory; a film of July 17 (Fig. 4) showed some clearing, and this seemed at the time to substantiate the diagnosis of tuberculosis.

A month later he complained of a mild sore throat, his first symptom of any kind since he was first seen. X-ray (Fig. 5, August 21) showed a large fresh opacity just above the lesser fissure; there was again considerable eosinophilia and eosinophils were found also in the sputum. A week later, another film was taken (Fig. 6, August 28) and this showed almost complete clearing on the right side, but a small new opacity was seen in the left second interspace.

On September 18 he completed three months' chemotherapy, and a routine film was taken (Fig. 7). This was entirely normal. The diagnosis of tuberculosis was therefore in considerable doubt, although it must be admitted that the opacities in the left upper zone (with exception of the small opacity in the second interspace seen only in Fig. 6) had behaved somewhat differently from the other lesions.

A month later he was to have been discharged, but he then complained of mild malaise and had a slight evening fever. A film (Fig. 8, November 7) showed a very large opacity in the right lower zone (an intervening film a week previously had still been normal). There was the usual eosinophilia. He was treated with phenergan 25 mg. at night, and made a rapid symptomatic recovery. His X-ray showed considerable clearing in a fortnight and he was discharged from hospital; a fortnight later the film was normal. He is continuing to take phenergan, and feels very well.

The final diagnosis in this case is presumed to be pulmonary eosinophilia, and the diagnosis of tuberculosis has been discarded.

Discussion

In the series of cases described by Crofton *et al.* (1952) the radiographic changes in the cases of simple pulmonary eosinophilia (sub-group (i)) were usually fan-shaped and fairly homogeneous, but with indefinite borders; but were occasionally nodular (Benda and Weinberg, 1940) or rounded (Leitner 1941). In the present case Figs. 5 and 8 show the former type of opacity, while Figs. 1 and 6 show the latter.

Again, in Crofton's series (1952) the radiographic changes in prolonged pulmonary eosinophilia (sub-group (ii)) were bilateral at some stage in the majority of cases, and in most instances successive shadows were observed; one infiltration would resolve to be replaced by others on the same or the opposite side. In only one case was it clear that the same shadow persisted throughout (Kartagener, 1942). The present case is, therefore, of some rarity in that the prolonged shadow was the same throughout.

Since, as shown by Rose and Spencer (1957), several years may elapse between episodes of pulmonary eosinophilia and frank polyarteritis nodosa,

PLATE XIX

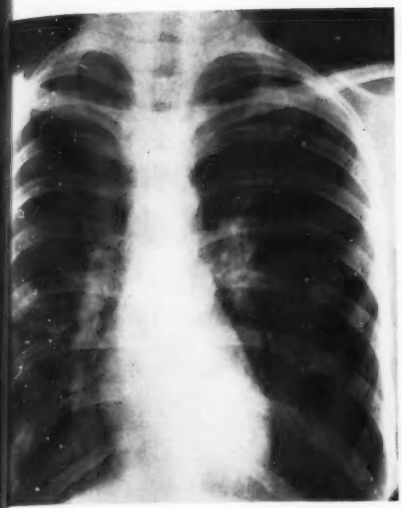

FIG. 1.—Opacities in right mid-zone and left upper zone.

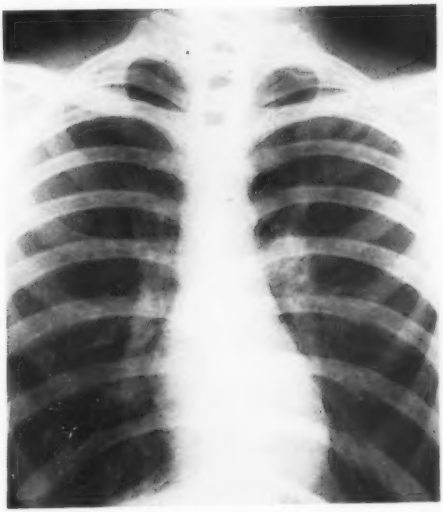

FIG. 2.—Eight days later. Right mid-zone now clear, but left upper zone unchanged.

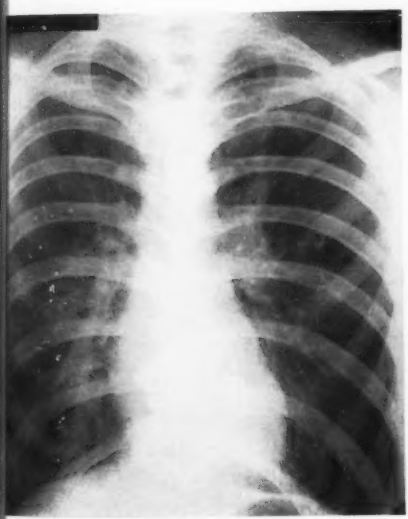

FIG. 3.—Two weeks later. No further change.

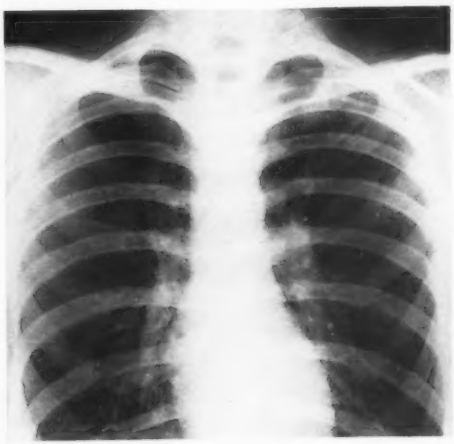

FIG. 4.—After one month on chemotherapy. Some clearing.

To face p. 132

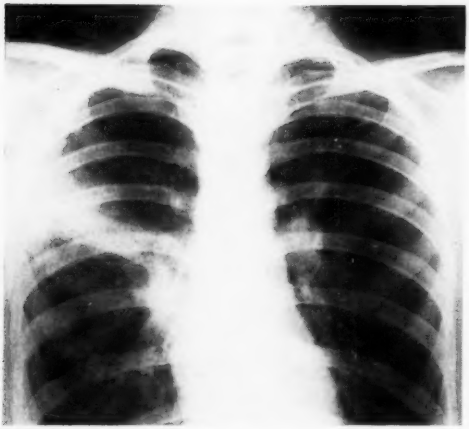

FIG. 5.—Five weeks later. Large new opacity just above lesser fissure. No great change in left upper zone.

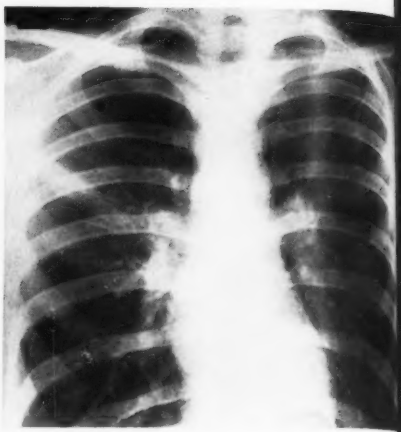

FIG. 6.—One week later. Right side shows ma clearing. Small new nodular opacity in left sec interspace.

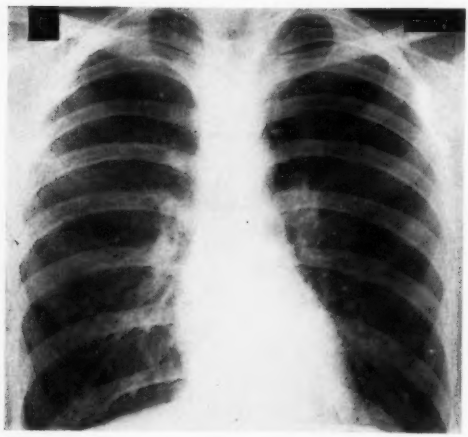

FIG. 7.—Three weeks later (still on chemotherapy). Normal film.

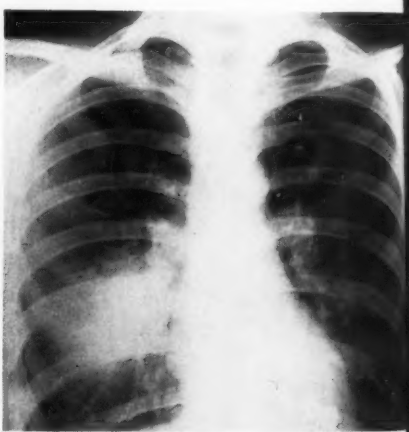

FIG. 8.—Seven weeks later. Very large opacity right lower zone.

there remains the possibility that what happened in this patient's chest is the prelude to this disease. Ellman (1956) reported some cases of eosinophilic polyarteritis, but they had much higher total white counts and eosinophil counts than the patient just described; on the other hand, they were clearly at a much later stage of the disease.

Summary

A case of pulmonary eosinophilia is presented, showing the occurrence of all the known kinds of radiographic changes associated with this condition in its simple form; and at the same time a shadow was present for several months which is presumed to have been due to prolonged pulmonary eosinophilia, but was unusual in that the same shadow persisted throughout.

There is a possibility that this episode may be the prelude to a generalised polyarteritis nodosa.

I wish to thank Dr. A. S Herington, Consultant Physician in charge of this patient in hospital, for very kindly making available to me his notes and X-rays. Dr. R. Ollerenshaw, Department of Medical Photography, Manchester Royal Infirmary, very kindly made excellent copies of the X-rays for publication purposes. The Librarian of the British Medical Association was invaluable in finding and checking the references.

My thanks are also due to Dr. F. E. Joules, Physician Superintendent, Milford Chest Hospital, and Dr. A. Sakula, Consultant Chest Physician, Redhill Chest Clinic, for permission to publish this case.

REFERENCES

Benda, M. R., and Weinberg, L. (1940): *Bull. Soc. med. Hôp., Paris*, **56**, 24.
Crofton, J. W., Livingstone, J. L., Oswald, N. C., and Roberts, A. T. M. (1952): *Thorax*, **7**, 1.
Ellman, P., and Cudkowicz, L. (1954): *Thorax*, **9**, 46.
Ellman, P. (1956): *Postgrad. med. J.*, **32**, 370.
Kartagener, M. (1942): *Schweiz. med. Wschr.*, **72**, 862.
Leitner, S. J. (1941): *Ergebn. ges. Tuberkforsch.*, **10**, 277.
Rose, G. A., and Spencer, H. (1957): *Quart. J. Med.*, 50, 43.

UNUSUAL LESIONS OF THE RIGHT DIAPHRAGM

A REPORT OF TWO CASES

By M. Meredith Brown

Milford Chest Hospital, Surrey

The region of the diaphragm often presents difficulties in the interpretation of chest skiagrams, while the increasing use of thoracic radiology has led to more frequent recognition of diaphragmatic abnormalities. These are presumably congenital in origin, or at least cannot be shown to be due to acquired disease. Symptoms are usually absent, or if present are due to an unrelated cause. Treatment is usually unnecessary, but it is important to make an accurate diagnosis, in order to exclude neoplastic or other serious disease. Two illustrative cases were seen at this hospital within a month. Exact diagnosis was made in the first by simple measures, but an exploratory operation was done in the second.

Case 1. A housewife aged 35 attended a Mass Miniature Radiography unit where a round opacity was seen in the right lower chest (Fig. 1, Plate XXI). She was referred for investigation and possible thoracotomy. She complained of no symptoms and admitted to none on questioning. She had two healthy children, and had previously attended for mass radiography on six occasions at yearly intervals, the last being three years previously, no abnormality being reported.

Her present skiagram showed a uniform roundish shadow the size of a tangerine lying just above the right diaphragm and seen in the lateral view to be closely related to the apex of its dome. Screening showed normal movements.

In order to outline the diaphragm more clearly, a diagnostic pneumoperitoneum was induced with 1 litre of air (Fig. 2, Plate XXI). The patient felt "pulling in her shoulder." On screening the lesion was no longer visible. The following morning screening was repeated, with a view to a refill. A small pneumoperitoneum was still present, but there was now, in addition, a right pneumothorax (Figs. 3 and 4, Plate XXI). The lesion was seen as before. It was thought that there was free communication between peritoneal and pleural cavities, and that the shadow was due to a reducible liver hernia.

Advantage was taken of the pneumothorax, and a thoracoscopy was done under local anæsthetic. The findings were as follows: "There was a mushroom-shaped piece of liver coming through the middle of the central tendon of the diaphragm. The hole was smaller than the piece of liver, so its edges could not be seen. It lay just lateral to a vertical fatty fold which probably contained the phrenic nerve and vessels. The diaphragm and liver appeared normal. The piece of liver was about 4 cm. in diameter and the opening about 2 cm., at the apex of the dome of the diaphragm" (Fig. 5).

The appearances suggested a congenital hernia, and no history of trauma could be obtained.

After considerable deliberation it was decided not to advise surgical

(*Received for publication October* 12, 1956.)

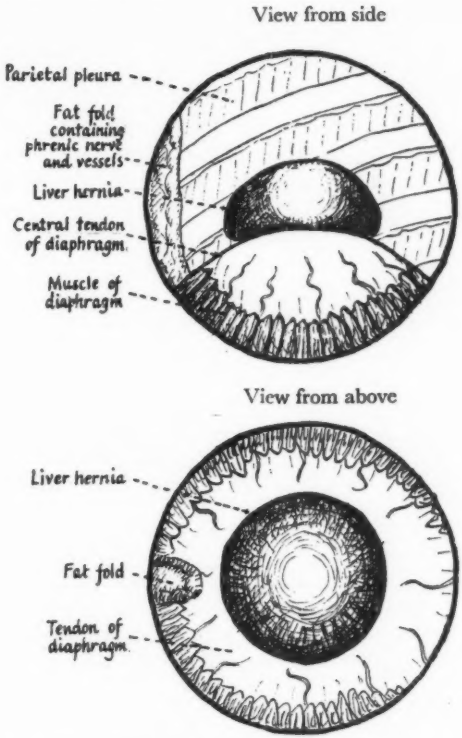

FIG. 5 (CASE NO. 1).—APPEARANCES AT THORACOSCOPY

treatment, as there were no symptoms, as strangulation seemed unlikely and as the position of the hernia meant that bowel was very unlikely to enter it. The position was explained to the patient and she was advised to remain under observation, and that operation would be indicated if the hernia became larger. Nine months later her radiograph was unchanged.

Discussion: The development of the diaphragm is complicated. Although the muscle is derived from the third and fourth cervical myotomes, elements from the septum transversum, the dorsal and ventral mesenteries all join to form the diaphragm, which is complete by the third month. The dome of the diaphragm is generally believed to be a fusion area (d'Abreu, 1953), though Mayer (1950) denies this. A small defect may be left, and a hernia develop subsequently, which in such a case will have no peritoneal sac. The absence of sac in this patient was shown by the free passage of air from peritoneum to pleura. An acquired hernia over the base area of the liver, which lies posteriorly, would also be expected to have no sac. That the hernia had not been demonstrated by several previous miniature radiographs, which was confirmed by rescrutiny, may have been due to its reducibility, which was demonstrated on this occasion. Four years previously a full-sized film had been taken. On re-examining this, a slight irregularity of the right diaphragm was visible.

A similar case was reported by Evans and Simpson (1950) in a boy aged 14 treated by operation. That of Clay and Hanton (1951), also treated surgically, lay posteriorly and was larger. There was an associated aberrant lung artery. They point out that air from a pneumoperitoneum will not outline a liver hernia from the bare area. The right diaphragmatic hernia reported by Cruickshank (1952) in this Journal contained kidney, not liver. Hollander and Dugan (1955) described four cases of herniation of liver through the right diaphragm. In each there was a past history of severe trauma to the right lower chest. The lateral radiograph showed a characteristic mushroom-like shadow, as in this patient.

Unfortunately the lesson learnt in this case of the value of diagnostic pneumoperitoneum was not applied to the second.

Case 2. A commercial traveller aged 57 complained of tiredness for about six months and of shortness of breath for four weeks; both symptoms were of gradual onset. His weight was stationary, and he had occasional cough with a little mucoid sputum. No abnormality was found on examination. His chest radiograph was interpreted as showing a right encysted effusion. An attempted aspiration produced a few cubic centimetres of bloodstained fluid, which on examination showed 70 per cent. lymphocytes and 30 per cent. polymorphs, and was sterile on culture. His blood count gave a total of 15,000 leucocytes and 84 per cent. polymorphs. He was kept under observation and remained well, but became easily dyspnœic. Several further attempts at aspiration were unsuccessful, but finally a few cubic centimetres of bloodstained fluid were again withdrawn. His radiographs were unchanged (Figs. 6 and 7, Plate XXII). On screening no movement of the right hemidiaphragm was seen. His Mantoux reaction was positive.

Bronchoscopy showed an anatomical abnormality of the right bronchial tree but no other lesion. The upper lobe bronchus divided into two large branches, which divided again. The middle lobe bronchus was large. The lower lobe bronchus was small and appeared to have three divisions. A bronchogram confirmed these findings (Fig. 8, Plate XXII).

The diagnosis of encysted pleural effusion was agreed to, and in view of the persistence of the dyspnœa and the radiological change thoracotomy was advised and accepted, especially as the suspicion of cancer had been aroused.

At operation the right chest was opened by resection of the sixth rib (Fig. 9). An incision made in the usual way in the rib bed entered the abdominal cavity and exposed the liver. There was no pleural effusion. The shadow seen in his radiographs was caused by the anterior half of his diaphragm, which was very high, so that the liver underneath the diaphragm lay much higher than usual, causing the shadow thought to be an effusion. The diaphragm was in two distinct parts, the inner part being the high one and the two being separated by a ridge of thickened muscle. It resembled but was not, in fact, a partial eventration, because the musculature of the diaphragm appeared normal. The phrenic nerve was normal. No movements of the diaphragm were seen, but this was due to the anæsthetic. Except for a white scar on its surface the liver appeared normal. The scar lay along the ridge at the top of the piece of the liver beneath the abnormal diaphragm. The anatomy of the lung was abnormal. The usual fissures were not present. There was a superficial fissure on the lateral surface of the lung in a more anterior position than the normal oblique fissure. Anterior to this fissure there was no pleural cavity, probably from a congenital

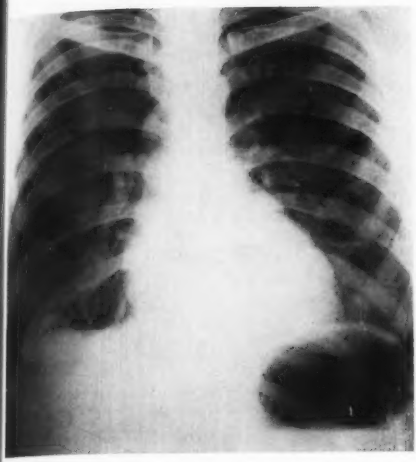

FIG. 1.—(Case No. 1.) Plain P.A. radiograph of chest.

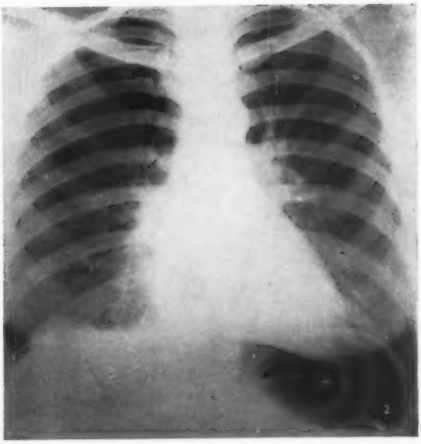

FIG. 2.—(Case No. 1.) After induction of pneumoperitoneum

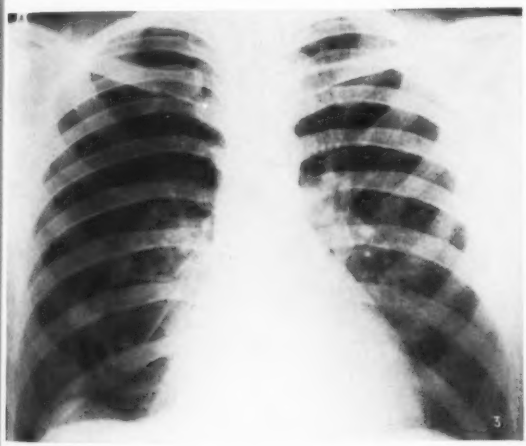

FIG. 3.—(Case No. 1.) Pneumoperitoneum has disappeared and a right pneumothorax is now present.

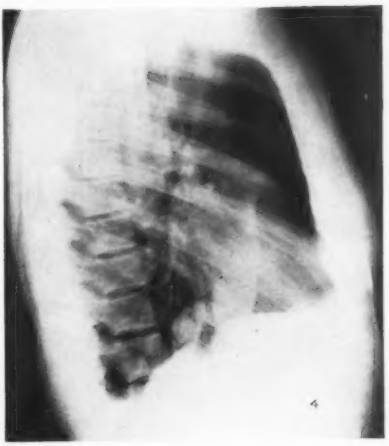

FIG. 4.—(Case No. 1.) Right lateral radiograph on same occasion as Fig. 3, showing the mushroom shape of the lesion.

To face p. 136

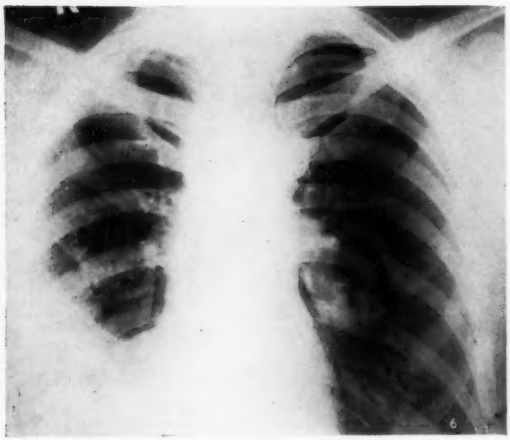

FIG. 6.—(Case No. 2.) P.A. radiograph of chest.

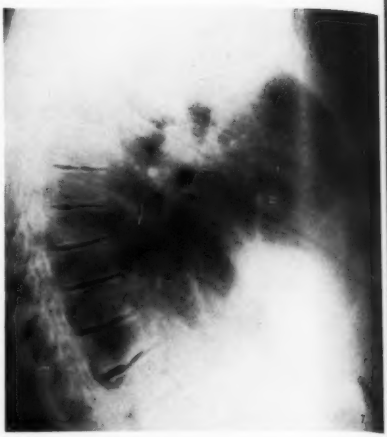

FIG. 7.—(Case No. 2.) Right lateral radiograph of chest.

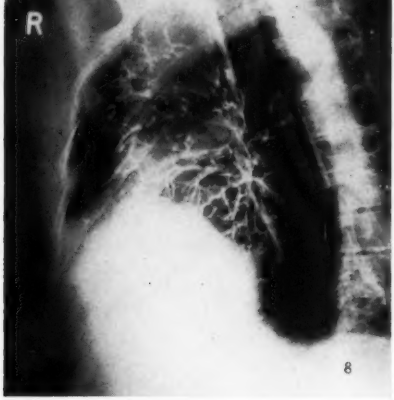

FIG. 8.—(Case No. 2.) Oblique view of right bronchogram showing anatomical abnormality.

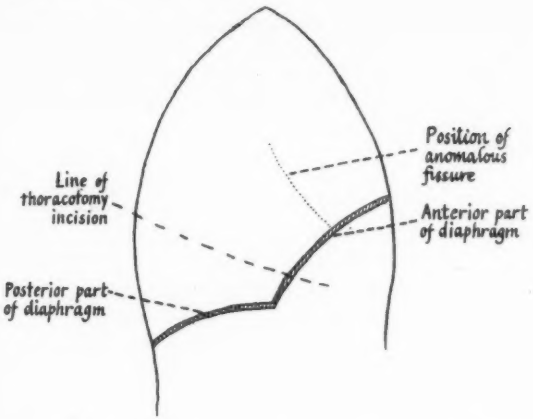

FIG. 9 (CASE NO. 2).—DIAGRAM OF A LATERAL SECTION OF RIGHT CHEST

absence rather than from pathological adhesions. Running in the fissure was an abnormal pulmonary vein, receiving tributaries from both sides of the fissure (Fig. 10). This left the lung and ran in a small fold of pleura to enter the pericardium. The free portion of the vein was about 3 cm. long and the vein was 5 or 6 mm. in diameter. Within the fold of the pleura were several small lymph glands; these were normal. One was sent for histology and later reported as showing changes of chronic inflammation only. This vein entered the pericardium anterior to the inferior pulmonary vein. The latter vessel appeared of the normal size and position. The entry of the anomalous vein was in line with the superior vena cava and in fact it looked as though it was entering the right atrium rather than the left. As there was no clinical evidence of this no further examination of the vein's termination was done. There were no adhesions over the posterior part of the lung. There were one or two fine nodules near the apex which may have been healed tubercles. There was no evidence of any active pathological lesion found. The condition was a congenital anomaly.

The patient made an uneventful recovery and was relieved of his anxiety and symptoms.

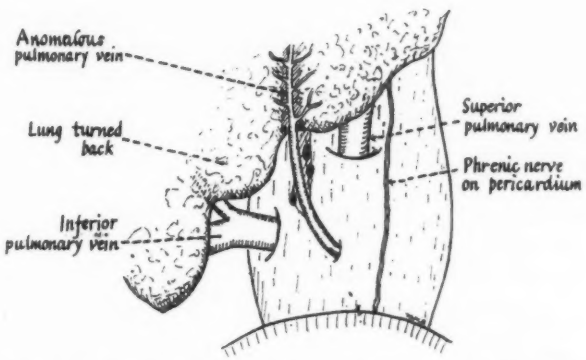

FIG. 10 (CASE NO. 2).—SKETCH OF THE FINDINGS AT OPERATION

In this case, had suspicions of a congenital abnormality been aroused—as they should have been by the state of the bronchial tree, the unchanging skiagram and the failure to aspirate genuine pleural fluid—the true position of the diaphragm and the cause of the unusual shadow would have been demonstrated by pneumoperitoneum and thoracotomy avoided.

Discussion: The multiple abnormalities suggest a minor error occurring early in development with a failure of descent of those parts of the cervical myotomes which go to form the anterior part of the diaphragm with tissue from the septum transversum and ventral mesentery.

I have been unable to find a report of any similar case.

Roe and Stephens (1956) point out that congenital diaphragmatic hernia is often associated with hypoplasia of the lung. Minor congenital anomalies may be similarly associated, as in this case.

Summary

Two cases illustrating unusual lesions of the right diaphragm are recorded. The first case showed that the uniform rounded shadow above the right diaphragm was due to a herniation of liver through the right diaphragm. In the second case, initially thought to be due to an encysted effusion, the raised right diaphragm was due to a congenital anomaly associated with a congenital abnormality of the right bronchial tree. The value of a diagnostic pneumoperitoneum is illustrated.

REFERENCES

Clay, R. C., and Hanton, C. R. (1951): *J. thorac. Surg.*, **21**, 57.
Cruickshank, G. (1952): *Brit. J. Tuberc. Dis. Chest*, **46**, 223.
d'Abreu, A. L. (1953): "A Practice of Thoracic Surgery." London: Arnold.
Evans, C. J., and Simpson, J. A. (1950): *Thorax*, **5**, 343.
Hollander, A. G., and Dugan, D. J. (1955): *J. thorac. Surg.*, **29**, 357.
Meyer, H. W. (1950): *J. thorac. Surg.*, **20**, 235.
Roe, B. B., and Stephens, H. B. (1956): *J. thorac. Surg.*, **32**, 279.

SERIAL SERUM PROTEIN CHANGES IN PULMONARY TUBERCULOSIS

By P. O. Leggat

From the Chest Clinic, Newcastle upon Tyne

For many years the only method available for the study of simultaneous changes in all the protein fractions of the plasma or serum was that of Tiselius (1937). It suffered from the disadvantage that the apparatus was costly, difficult to maintain, and in operation time consuming. With the advent of paper electrophoresis, the method became feasible for ordinary hospital clinical laboratories. The method was relatively simple and the apparatus robust. However, it must be realised that the method, although much easier than the moving boundary technique in a liquid phase of Tiselius, is still fairly time consuming.

Method

The total protein of the serum is estimated by means of standard copper sulphate solutions of varying specific gravities (Phillips *et al.*, 1944). Serum is used in preference to plasma as it avoids the confusion caused by the fibrinogen band lying between the beta and gamma globulin bands.

With a micro pipette 0·01 or 0·02 c.c. of serum is placed in the centre of a strip of Whatman No. 1 filter paper (2 by 32 cm.). The strip is then damped with Veronal Buffer *p*H 8·6 and placed on a slightly inclined plane in an open strip paper electrophoresis apparatus with platinum electrodes. A current of 20 ma. at 120 v. is applied for eighteen to twenty-four hours. The protein fractions migrate at different rates towards the anode. The strip is thoroughly dried and the protein fixed in a hot-air oven at 90° C. Subsequently it is stained for ten minutes with a saturated solution of naphthalein black in methyl alcohol, decolorised with 10 per cent. glacial acetic acid in methyl alcohol and finally rinsed in pure methyl alcohol. The density of the various protein bands is read on a semi-automatic recording densitometer (Latner and Rose, 1954). Finally the areas below the curves are calculated.

Material

Eighteen cases of adult pulmonary tuberculosis have been studied. Nine of the cases were far advanced, seven moderately advanced and two minimal. Tubercle bacilli were isolated from the sputum in sixteen out of the eighteen cases on at least one occasion. Tuberculous abscess cavity formation was present in twelve of the cases. Six of the cases failed to respond or showed evidence of deterioration, in spite of treatment. All the cases were treated with various combinations of Streptomycin, PAS (para-aminosalicylic acid) or Isoniazid. In two of the cases a pneumoperitoneum was induced.

(*Received for publication February* 7, 1957.)

The cases were studied for an average of 34·13 weeks within a maximum range of 24 weeks to 36 weeks.

On taking the means of the twelve patients who improved, the total protein, after a preliminary fall, rose slowly. Concurrently, the levels of the alpha 1, alpha 2 and beta globulins progressively fell. The albumin/alpha 2 ratio rose steadily and reached normal values before the albumin. (Table 1.)

TABLE 1.—SATISFACTORY CASES
Mean values for serum proteins g. %.

Weeks	*Total protein*	*Albumin*	*Alpha 1 globulin*	*Alpha 2 globulin*	*Beta globulin*	*Gamma globulin*	*Albumin/ Alpha 2 globulin*
0 (12)	6·81	3·1	0·485	0·791	1·016	1·47	3·92
4 (12)	6·45	3·1	0·40	0·665	0·79	1·46	4·64
8 (12)	6·65	3·3	0·304	0·75	0·885	1·36	4·4
12 (10)	6·73	3·54	0·467	0·666	0·784	1.29	5·23
16 (6)	6·7	3·3	0·275	0·603	0·87	1·65	5·48
20 (8)	6·9	3·9	0·308	0·597	0·79	1·37	6·55
24 (5)	6·8	3·98	0·392	0·465	0·746	1·23	8·55
28 (7)	6·64	3·76	0·301	0·47	0·655	1·21	8·00
32 (2)	6·95	4·38	0·265	0·578	0·765	1·02	7·6
36 (4)	7·11	4·01	0·273	0·573	0·868	1·405	7·00

Figures in parenthesis are the number of cases.

In the six unsatisfactory cases, the mean total protein level rose fairly steeply from the start. This was associated with a rise in the albumin, alpha 2, beta and gamma globulins, and a fall in the alpha 1 globulin in the first four weeks. The albumin levels never reached normal values. The albumin/alpha 2 ratio shows an erratic rise and never reaches normal values. (Table 2.)

Case Report

G.P., aged 42 years. Bilateral cavitary disease, five zones involved. Five months in hospital. While he was in hospital he was treated with Streptomycin 1 G. per day up to a total of 120 G. of Streptomycin covered by Isoniazid 200

mg. per day. For the last four weeks in hospital he was treated with PAS 12 G. per day with Isoniazid 400 mg. There is an initial fall in the toal protein and albumin followed by a sustained rise for twenty-two weeks. After a preliminary fall for eight weeks, the albumin/alpha 2 ratio rises progressively for sixteen weeks. (Fig. 1.) Nine out of the eighteen cases showed this initial fall in the serum protein and albumin over the first four to eight weeks. Four weeks after the patient's discharge from hospital a serious clinical and radiological deterioration occurred, and this was associated with a considerable fall in the albumin/alpha 2 ratio. (Fig. 1.)

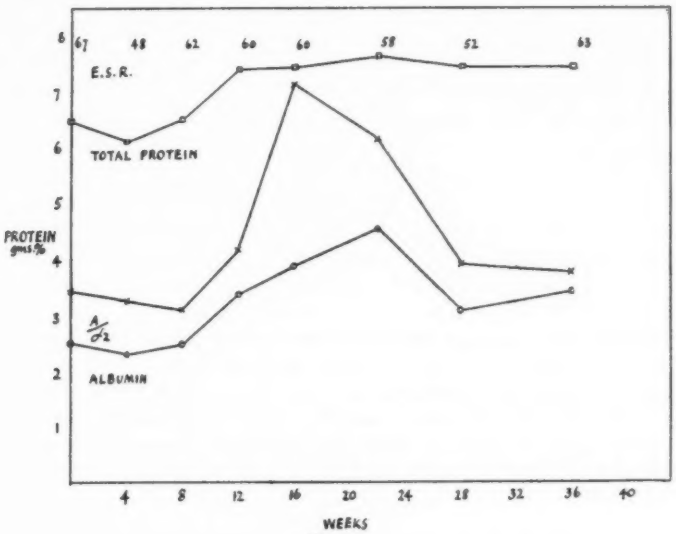

FIG. 1

J.L., aged 67 years. Moderately extensive bilateral cavitary disease involving three zones. Fifteen weeks in hospital. During the time in hospital he was treated with Streptomycin 1 G. per day up to a total of 60 G. of Streptomycin; this was covered by Isoniazid 200 mg. per day. Immediately prior to discharge the patient was started on PAS 12 G. per day, covered by Isoniazid 400 mg. per day. This drug dosage was continued as an out-patient.

There is a fairly sharp initial rise over the first four to eight weeks in the total serum protein and albumin, followed by a slight fall, then a more sustained rise, which is continued for twenty-eight weeks. The albumin/alpha 2 ratio follows the contours of the albumin and the total protein. At the twenty-eighth week serious clinical and radiological deterioration occurred associated with a fall in the total protein, albumin and albumin/alpha 2 ratio. (Fig. 2.) Five of the cases showed this type of initial total protein, albumin pattern.

J.S., aged 66 years. Extensive bilateral disease involving five zones. The patient was twelve weeks in hospital, and during this time he was treated with Streptomycin 1 G. per day covered by Isoniazid 200 mg. per day, up to a total of 21 G. of Streptomycin. This treatment was followed by PAS 12 G. per day with 400 mg. of Isoniazid, which was continued after his discharge from hospital. He remained clinically and radiologically well, with a negative sputum.

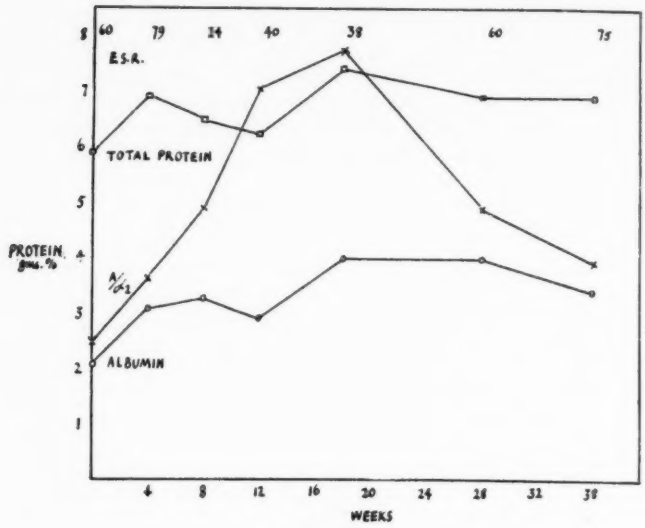

FIG. 2

There is a fairly marked fall in the total protein over the first eight weeks, while over the same period the albumin shows a slight initial rise followed by a fall, then a further sustained rise. Up to the twenty-fifth week the albumin/alpha 2 ratio follows the same pattern, and then decreases rapidly owing to an increase in the alpha 2 globulin, although the patient remained well. (Diagram 3.) Four of the cases showed this primary fall in the total protein, with a rising albumin.

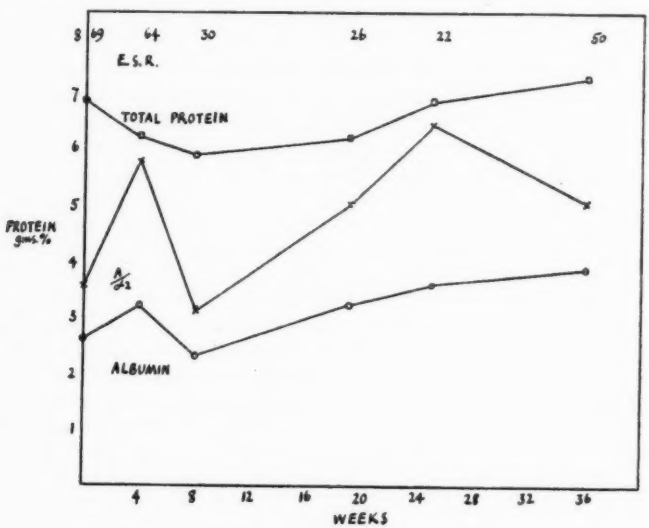

FIG. 3

Discussion

Throughout this paper I have taken as a standard of normal the figures quoted by Gilliland *et al.* (1956). These authors quote the mean of 28 normals as: protein 7·27 G. %, albumin 4·15 G. %, alpha 1 globulin 0·29 G. %, alpha 2 globulin 0·59 G. %, beta globulin 0·83 G. %, gamma globulin 1·4 G. %, and albumin/alpha globulin ratio 7·06. As will be noted from Diagrams 1, 2 and 3, there is no evidence of any correlation between the E.S.R. and the protein fraction levels including the albumin/alpha 2 ratio. In seven out of eighteen undoubtedly active cases the E.S.R. was initially normal. This lack of correlation is probably because the E.S.R. mainly depends upon fibrinogen levels (Fahreus, 1921). Alpha 2 levels have a moderate effect, while beta and gamma globulin levels have only a slight effect on the E.S.R.

Wetmar (1954) demonstrated in experimental tuberculosis in rabbits the lowering of the albumin and the raising of the alpha and beta globulin levels.

Weimar (1954) showed that very similar changes occurred in the serum proteins of guinea-pigs infected with tuberculosis, but also noted that there was a rise in the total protein with active disease.

Abraham (1954) states in man the albumin is low and the alpha 2, beta and gamma globulins are high in active tuberculosis. With improvement in the patient's condition, the fractions return to normal.

Siebert (1943), Volk (1953), Baldwin *et al.* (1953), all state that the gamma globulin is raised in active disease, while Flynn (1954) is of the opinion that this is not always the case. Houston *et al.* (1954) by means of viscosimetry estimated that in 68 per cent. of cases with active disease the gamma globulin is raised. My own findings show that it is not frequently raised in active disease.

Baldwin *et al.* (1953) is of the opinion that the beta globulin is not always increased in active disease, and in this I agree, as six cases out of the eighteen had normal levels to start with.

Volk (1953) noted that in some cases the alpha 2 globulin and beta globulin levels remained raised after clinical arrest. Certainly in case J.S. (Diagram 3) the alpha 2 level remained abnormally high, although the patient was well and the albumin continued to rise.

Gilliland *et al.* (1956) in a careful statistical review of 327 cases of adult pulmonary tuberculosis, with a single estimation carried out on each individual, clearly demonstrated that in active disease the albumin fraction was low, and the alpha 2 globulin high, with the result that the albumin/alpha 2 ratio was also abnormally low. In cases under treatment and healed cases these values were normal or approached normal. The authors emphasised the value of the albumin/alpha 2 ratio in estimating progress. There would appear to be no doubt that as healing occurs there is a steady and progressive rise in this ratio. (Table 1.) It is also to be noted that in the unsatisfactory group of cases this ratio never reaches normal values. (Table 2.) With satisfactory progress, the total protein also shows a steady rise. (Table 1.) The albumin/alpha 2 ratio may be a more sensitive index of deterioration than consideration of the albumin alone, as in case G.P. (Diagram 1) and case J.I. (Diagram 2) the ratio decreased before there was any fall in the albumin.

A common finding in all the eighteen cases was a very low initial albumin figure and a high alpha 2 figure with a low albumin/alpha 2 ratio. These

TABLE 2.—UNSATISFACTORY CASES
Mean values for serum proteins g. %.

Weeks	*Total protein*	*Albumin*	*Alpha 1 globulin*	*Alpha 2 globulin*	*Beta globulin*	*Gamma globulin*	*Albumin/ Alpha 2 globulin*
0 (6)	6·34	2·75	0·643	0·746	0·886	1·5	3·67
4 (6)	6·8	2·9	0·385	0·88	1·04	1·62	3·3
8 (6)	6·7	3·07	0·428	0·83	0·946	1·45	3·7
12 (5)	6·88	3·32	0·33	0·71	0·946	1·75	4·67
16 (4)	6·82	3·36	0·354	0·585	0·92	1·63	5·7
20 (4)	7·13	3·44	0·44	0·763	0·97	1·45	4·53
24 (2)	7·3	3·72	0·31	0·765	0·945	1·58	4·86
28 (3)	7·34	3·75	0·343	0·764	0·95	1·59	4·91
32 (2)	6·4	3·4	0·41	0·630	0·775	1·17	5·4
36 (2)	6·84	3·53	0·553	0·640	0·825	1·29	5·46

Figures in parenthesis are the number of cases.

values returned towards normal over a period of months, as healing of the disease occurred. There is a rapid fall in the albumin level whenever clinical deterioration occurs, but it would appear that even this has its exceptions, as in one case there was a marked fall in the albumin and a slight fall in the total protein although the disease remained soundly healed. Alpha 2 globulin was raised initially in fifteen and gamma globulin in ten out of the eighteen cases.

Estimation of albumin levels or albumin/alpha 2 ratio might therefore be an attractive method for estimating activity and following the progress of a case. Certainly a method other than the E.S.R. would be welcome in view of the lack of sensitivity of the latter. However, I do not think that filter paper electrophoresis is entirely suitable for routine use, mainly on account of the technical difficulties inherent in the method (Martin *et al.*, 1954), and the amount of time required to prepare and read the strips.

Summary

Filter-paper electrophoresis is discussed in relation to pulmonary tuberculosis.

Albumin levels and albumin/alpha 2 ratio are consistently low and alpha 2 globulin frequently raised in active disease. These values return towards normal as healing occurs.

Albumin levels and albumin/alpha 2 ratio always fall if the disease reactivates, but occasionally falls occur in what appear to be healthy people.

The albumin/alpha 2 ratio may be a more sensitive index than the albumin levels alone.

Although the method compares favourably with the E.S.R., in regard to degree of sensitivity, complexity of technique makes it difficult to apply as a routine method in all cases.

REFERENCES

ABRAHAM, B. (1954): *Amer. Rev. Tuberc.*, **70,** 344.
BALDWIN, R. W. (1955): *Amer. Rev. Tuberc.*, **68,** 372.
FAHREUS, R. (1921): *Acta. med. scand.*, **55,** 1.
FLYNN, F. V., and DE MAYO, P. (1951): *Lancet*, **261,** 235.
GILLILAND, I. C., *et al.* (1956): *Brit. med. J.*, **2,** 1460.
HOUSTON, J., *et al.* (1955): *Brit. J. Tuberc. Dis. Chest*, **49,** 119.
LATNER, A. L., MOLYNEAUX, L. and ROSE, D. J. (1954): *J. Lab. clin. Med.*, **43,** 157.
MARTIN, N. H., and FRENGLEN, J. (1954): *J. clin. Path.*, **7,** 87.
PHILLIPS, R. A., VAN SLYKE, D. D., DOLE, V. P., EMERSON, K., HAMILTON, P. B., and ARCHIBALD, R. M. (1944 and 1945): "Copper sulphate method for measuring the specific gravities of whole blood and plasma." Joshia Macy Jr. Foundation, N.Y.
SIEBERT, F. B. (1943): *Amer. Rev. Tuberc.*, **47,** 66.
TISELIUS, A. (1937): *Trans. Faraday Soc.*, **33,** 524.
VOLK, B. W. (1953): *Amer. Rev. Tuberc.*, **67,** 299.
WEIMER, E. H. (1954): *Amer. Rev. Tuberc.*, **70,** 344.
WETMAR, R. (1954): *Ophthalmologica (Basel)*, **127,** 315.

THE STRAIT-WAISTCOAT

AN EARLY UNRECOGNISED FORM OF COLLAPSE THERAPY

By Richard A. Hunter

Claybury Hospital, Woodford Green, Essex

AND

J. G. Widdicombe

From the Department of Physiology, Medical College of St. Bartholomew's Hospital, London

For centuries it has been held that there is an intimate relation between disease of the lungs and the state of the patient's mind. Here we are concerned with the clinical observations made in the late eighteenth and early nineteenth centuries which led to the belief that tuberculosis and insanity were to some extent incompatible and mutually exclusive. The view that these diseases alternated in some patients was held in England by " almost all writers on insanity, from Mead [1751] downwards " (Clouston, 1863), and persisted until the middle of the nineteenth century (Bucknill and Tuke, 1858). For instance, Burrows (1828) wrote: " there appears an interchangeable relation between lunacy and phthisis pulmonalis; the latter being cured by the accession of the former, and recurring as soon as the brain resumes its natural functions," although he admitted that " phthisis kills more than half the lunatics in La Salpêtrière." Although " many striking examples of consumption alternating with mania are upon record " (Southey, 1814), in most patients pulmonary consumption was relieved by the onset of insanity, and not vice versa. " It is remarkable," wrote Rush (1812), " that this disease [pulmonary consumption] does not so often suspend madness, as madness does pulmonary consumption," an observation also made by Burrows (*loc. cit.*) and Kolk (1863).

How did this belief originate, and what was the evidence for it? A possible explanation seemed to be contained in a case history reported by Southey (1814): " A case of hereditary consumption in its last stage was suddenly and perfectly suspended for some months by mental derangement. The patient was obliged to have a strait waistcoat, and a keeper from London. During this affection of the brain, the cough and all the pulmonary symptoms ceased; but upon the removal of the maniacal, the phthisical symptoms returned, and the patient died about two months afterwards."

Could it have been the strait-waistcoat rather than the " mental derangement " which " suddenly and perfectly suspended for some months " the pulmonary consumption? And did the removal of the strait-waistcoat after the " maniacal " symptoms had abated allow the " phthisical " symptoms to return? In fact, could the introduction into psychiatric practice of the strait-waistcoat as a form of treatment and restraint have caused the clinical improvement in patients with pulmonary tuberculosis, which was then wrongly ascribed to the advent of insanity? This hypothesis was tested (1) historically,

(*Received for publication October* 24, 1956.)

FIG. 1.—A strait-waistcoat of the early 19th century, as worn by patients at Hanwell Asylum. The 3 buckles allow for the attachment of a head-piece to restrain the patient further.

To face p. 147

by elucidating whether the life of the strait-waistcoat coincided with the belief that pulmonary tuberculosis and insanity were incompatible; and (2) experimentally, by ascertaining whether the strait-waistcoat by constricting the chest acted in effect as a form of collapse therapy of the lungs.

The History of the Strait-waistcoat in the Treatment of Insanity

"Everybody has heard of a strait-waistcoat," wrote Conolly (1850), "but, familiar as the name is, perhaps nine people out of ten have never chanced to see one. It is, in fact, simply a jacket, formed of strong ticking or canvas, and made to tie behind with five or six strings. The sleeves are prolonged to the length of about twenty inches beyond the tips of the fingers; so that (the arms being crossed over the chest) they can be carried round the body, and secured behind by tapes which are threaded through the extremities" (Fig. 1).

Introduced in the first half of the eighteenth century as an improvement on restraining the insane by handcuffs, leg-locks and chains, the term strait-waistcoat was, according to the Oxford English Dictionary, first used by Richardson (1753) in his novel *The History of Sir Charles Grandison:* "She threatened her then with the Strait Waistcoat, a punishment at which the unhappy Lady was always greatly terrified." However, this was not the first use of either the article or the word: for instance, in 1739 Alexander Cruden, of *Concordance* fame, had published an account of his being "Chained, Handcuffed, Strait-Wastecoated and Imprisoned . . . in Wright's Private Madhouse on Bethnal-Green."

That the use of strait-waistcoats did not become general until the latter part of the eighteenth century is shown by the fact that they were not mentioned in the psychiatric writings of the period, such as those of Robinson (1729) and Battie (1758), nor in the records of Bethlem or St. Luke's Hospitals where patients continued to be confined by other means.

Kraepelin (1918) mistakenly attributed the invention of the strait-waistcoat to Macbride (1772), who wrote: "No small share of the management of mad people consists in hindering them to hurt themselves, or do mischief to other persons. It has sometimes been usual to chain and to beat them, but this is both cruel and absurd; since the contrivance called the Strait Waistcoat, answers every purpose of restraining the patients, without hurting them." George III was thus restrained in 1788, and Cullen (1790) advocated its wider use: "restraint . . . is useful, and ought to be complete . . . the strait waistcoat answers every purpose better than any other that has yet been thought of." Percival (1803) wrote of the strait-waistcoat as one of the "improvements in modern practice." By 1792 the use of strait-waistcoats had become general: in that year Arnold ordered twenty for the twenty patients to be admitted into Leicester's new lunatic asylum.

Following the suggestion of Gardiner Hill (1837) and the epoch-making reforms of Conolly (1856) at Hanwell Asylum, all physical restraint of the insane was gradually abolished, so that by the 1860s even the strait-waistcoat had fallen into disuse.

Thus the period of time during which the strait-waistcoat was in general use coincides with the period of about 100 years during which the belief was current that insanity and tuberculosis were in some way incompatible.

Experimental Observations on the Effect of the Strait-waistcoat on Lung Volume

Three young healthy male subjects were selected, and their respiratory volumes measured by spirometry. Vital capacity, expiratory reserve and inspiratory capacity were measured in the sitting position with and without the strait-waistcoat on, and in one subject also in the supine position: results are shown in the table.

Subject	*Change in volume (ml., with percentage of normal values)*			
	*Vital capacity**	*Expiratory reserve†*	*Inspiratory capacity‡*	*Functional residual capacity§*
A (sitting) ..	−390 (−10%)	−360 (−23%)	−30 (−1%)	−800 (−24%)
A (recumbent)	−420 (−10%)	−100 (−13%)	−320 (−10%)	
B (sitting) ..	−390 (−11%)	−290 (−17%)	−100 (−4%)	−740 (−33%)
C (sitting) ..	−340 (−8%)	−690 (−43%)	+350 (+12%)	−530 (−21%)

* The maximal volume of gas which can be expired following a maximal inspiration.
† The maximal volume of gas which can be expired from the end-expiratory position.
‡ The maximal volume of gas which can be inspired from the end-expiratory position.
§ The volume of air in the lungs at the end-expiratory position.

In all subjects the vital capacity was reduced by approximately 10 per cent. and the expiratory reserve by 13-43 per cent. In two subjects the inspiratory capacity was slightly reduced, while in one the inspiratory capacity was increased, though by only half the reduction in expiratory reserve. Thus in all subjects respiration was shifted to the expiratory side. Functional residual capacity was measured by a modified nitrogen wash-out method. In all subjects it was reduced by 530-800 ml. (21-33 per cent.), which is considerably greater than the decrease in expiratory reserve found on spirometry. This suggests that the residual air also is considerably decreased. In all subjects the respiratory rate rose on application of the strait-waistcoat by 24-40 per cent. of the control value over the period of measurement of 5-7 minutes.

These results show that in the three subjects tested the wearing of a straight-waistcoat produced a collapse of the lungs of 530-800 ml., with a somewhat smaller reduction in vital capacity.

Subjectively these effects seemed to result partly from restricted expansion of the chest proper, and partly from compression of the epigastric region by the folded position of the arms (see figure).

Comparison with Artificial Pneumoperitoneum

Measurements of lung volumes in patients with pneumoperitoneum have been carried out by Wright *et al.* (1949), who found that functional residual capacity was reduced by a mean of 30 per cent. in 17 subjects in the standing position, with a smaller and less consistent reduction in the recumbent position. They also observed that the application of an abdominal binder in patients with artificial pneumoperitoneum caused a further reduction in functional residual

capacity of 0-200 ml. in three subjects. Our results show that wearing a strait-waistcoat reduced functional residual capacity to a comparable extent.

Thus the collapsing effect on the lungs of the strait-waistcoat is similar to that of an artificial pneumoperitoneum.

Conclusion

Review of the history of the use of the strait-waistcoat in psychiatric practice, and experimental observations on its effect on lung volume, suggest that the belief that insanity and tuberculosis were incompatible may have arisen in the eighteenth century in part from the then unrecognised therapeutic effect of collapse therapy in pulmonary tuberculosis. This also could explain why insanity was reported more often to halt the progress of pulmonary tuberculosis than pulmonary tuberculosis the progress of insanity.

Although it may be argued that the element of comparative rest enforced by the strait-waistcoat may itself have had a beneficial effect on pulmonary tuberculosis, the cases reported seem to have improved and relapsed too strikingly and too rapidly for this alone to have been responsible. It is suggested that the strait-waistcoat had a direct though unrecognised effect on the disease by collapsing the lungs in the same way as an artificial pneumoperitoneum, which according to Livingstone (1952) " has definite value, greater than bed rest alone in acute exudative disease, in varying types of disease unsuitable at the time for artificial pneumothorax treatment or for surgical collapse measures, and possibly in a proportion of far advanced cases."

Thus valid clinical observations gave rise to faulty beliefs because they were evaluated in terms of current faulty theories of pathology. The possible beneficial effect of the strait-waistcoat in pulmonary tuberculosis was explained in terms of " conversion " or " metastasis of diseases," or " exchanges of diseased action " (Jenner, 1822), and so lost. Had physicians been content to observe and to record this phenomenon instead of missing its significance by strait-waistcoating it into preconceived humoral theories of disease, collapse therapy of pulmonary tuberculosis might have been anticipated by more than a century. As it was, Forlanini (1894), commencing in 1882, developed artificial pneumothorax treatment independently of earlier observations such as those of Carson (1822), while Banyai (1933) accidentally stumbled on the therapeutic effect of artificial pneumoperitoneum in 1931.

Summary

The belief that tuberculosis and insanity were incompatible arose in the middle of the eighteenth century *pari passu* with the widespread use of the strait-waistcoat in psychiatric practice, and disappeared with its disuse in the middle of the nineteenth century. Evidence is presented that this belief may have arisen from the pneumoperitoneum-like effect of the strait-waistcoat, which may thus have constituted an unrecognised form of collapse therapy.

We thank Professor K. J. Franklin, F.R.S., Department of Physiology, Medical College of St. Bartholomew's Hospital, for encouragement and laboratory facilities; Dr. Ida Macalpine for helpful advice; and Mr. N. K. Harrison, of the Photographic Department, St. Bartholomew's Hospital, for the figure. The strait-waistcoat used in the experiments, kindly lent by the Wellcome Historical Medical Museum by courtesy of Dr. E. Ashworth Underwood, had been

worn by patients at Hanwell Asylum before the advent of Dr. J. Conolly and non-restraint in 1839. This work was done while one of us (R.A.H.) was in receipt of a grant for expenses from the Wellcome Trustees.

REFERENCES

ARNOLD, T. (1792): MS. *Sketch of the Preparations necessary for a Lunatic Asylum.* Leicester County Archives.

BANYAI, A. L. (1933): *Amer. J. med. Sci.*, **186,** 513.

BATTIE, W. (1758): "A Treatise on Madness." London.

BUCKNILL, SIR JOHN C., and TUKE, D. H. (1858): "A Manual of Psychological Medicine." London.

BURROWS, G. M. (1828): "Commentaries on the Causes, Forms, Symptoms, and Treatment, Moral and Medical, of Insanity." London.

CARSON, J. (1822): "Essays, Physiological and Practical." Liverpool.

CLOUSTON, Sir THOMAS S. (1863): *J. ment. Sci.*, **9,** 36.

CONOLLY, J. (1850): "Familiar Views of Lunacy and Lunatic Life." London.

CONOLLY, J. (1856): "The Treatment of the Insane without Mechanical Restraints." London.

CRUDEN, A. (1739): "The London-Citizen Exceedingly Injured." London.

CULLEN, W. (1790): "First Lines of the Practice of Physic." Vol. 4. Edinburgh.

FORLANINI, C. (1894): *Gazz. med., Turin,* **45,** 381.

HILL, R. GARDINER (1837): Quoted by W. M. Pierce: "State of the Lincoln Lunatic Asylum." Lincoln.

JENNER, E. (1822): "A Letter to Charles Henry Parry . . . on the Influence of Artificial Eruptions." London.

KOLK, J. L. C. S. VAN DER (1863): "The Pathology and Therapeutics of Mental Diseases." Translated by J. T. Rudall. London, 1870.

KRAEPELIN, E. (1918): "Hundert Jahre Psychiatrie." Berlin.

LIVINGSTONE, J. L. (1952): The Use of Artificial Pneumothorax, Phrenic Paralysis, Pneumoperitoneum and Oleothorax. In "Modern Practice in Tuberculosis." Edited by T. Holmes Sellors and J. L. Livingstone. Vol. 2. London.

MEAD, R. (1751): "Monita et Praecepta Medica." London.

MACBRIDE, D. (1772): "A Methodical Introduction to the Theory and Practice of Physic." London.

PERCIVAL, T. (1803): "Medical Ethics." Manchester.

RICHARDSON, S. (1753-4): "The History of Sir Charles Grandison." Vol. 3. London.

ROBINSON, N. (1729): "A New System of the Spleen, Vapours, and Hypochondriack Melancholy." London.

RUSH, B. (1812): "Medical Inquiries and Observations, upon the Diseases of the Mind." Philadelphia.

SOUTHEY, H. H. (1814): "Observations on Pulmonary Consumption." London.

WRIGHT, G. W., PLACE, R., and PRINCI, F. (1949): *Amer. Rev. Tuberc.*, **60,** 706.

TUBERCULOSIS CONTACT FIRMS' SURVEYS

By F. A. Nash

South-west London Mass X-ray Service, Western Hospital, London, S.W.6

Case finding by the examination of the works contacts of new cases of tuberculosis found by the chest clinics is a neglected and almost unexplored field.

Definition. In the present context a contact firm means a place of employment at which a case of tuberculosis has recently occurred among the staff. Included among members of the staffs of such contact firms will be the works contacts of the new cases.

Definition. By the " works contacts " is here meant those people who have been exposed to the risk of being infected by, or passing infection to, the index case. Clearly not all employees of contact firms are works contacts, but all works contacts are employees of contact firms. (This statement does not cover contacts at work who are " casual " contacts—*e.g.*, from outside firms.) Works contacts are not administratively identifiable and indeed are difficult to identify even if detailed local epidemiological enquiries could be made, which for reasons of secrecy is not possible.

In the surveys described here there were two sources of information about the identity of contact firms, (*a*) the chest physicians participating in a contact firm intimation scheme, and (*b*) the managements or medical officers of firms.

(A) *Contact Firm Intimation Scheme*

Intimations were sent to the director of the mass X-ray unit by chest physicians when a case of pulmonary tuberculosis had been notified by them and had been last working at the firm specified. Accordingly, the firms were offered mass radiography in the usual way *without divulging that there existed a special reason for wishing to visit them.*

Details are now available of thirty-two firms visited at chest physicians' requests up to 31.12.1955. *Very few of these firms would have been visited for routine mass radiography had the unit not been guided to them by the " works contact " intimation scheme.* They employed in all 12,326 people. About two-thirds of the firms employed less than 300 people. In all 63 per cent. of the 12,326 employees were X-rayed. Among the 7,763 examined 85 people were found to have " radiological lesions, probably tuberculous, significant for chest clinic supervision " (*Code " D/TO " in the following paragraphs*), that is 1·1 per cent. of those examined.

(B) *Requests from Contact Firms*

All firms in the area covered by the South-west London Mass X-ray Service were asked to approach them whenever a " case of tuberculosis " occurred in

(*Received for publication November 14, 1956.*)

their workplace. Nineteen establishments were visited as tuberculosis contacts at their own request. They employed 11,107 people in all. Of this number 62 per cent. were X-rayed. Among these (6,901) people, 49 were found to have lesions coded D/TO. This is a yield of 0·7 per cent. of those examined.

Descriptive Procedure

In the description that follows the surveys have been divided into contact firms that are " high yield "—that is, firms with 0·5 per cent. or more examinees coded D/TO—and " low yield " contact firms, by which is meant firms with under 0·5 per cent. of examinees coded D/TO. The findings in these two groups will be compared with one another; they will also be compared (separately and combined) with the findings in 43,607 people examined by Unit 8C, an ordinary mobile unit visiting firms in the same area and in the same year of 1955.

Age/Sex Composition of Contact Firm Examinees compared with Ordinary M.R.U. Volunteer Populations

Table I shows that the age/sex composition of the contact firm employees is substantially similar to the composition of the routine mass X-ray population examined by Unit 8C in the same area in the same year.

The age/sex composition of high and low yield contact firms was also found to be similar in the two groups.

The proportions of examinees never previously X-rayed in contact firm employees was 44 per cent., while in ordinary M.R.U. volunteers the proportion never previously X-rayed was 26·5 per cent.

TABLE I.—AGE/SEX COMPOSITION OF CONTACT FIRMS' EXAMINEES COMPARED WITH UNIT 8C (ROUTINE M.R.U.)

	High yield		*Low yield*		*Total*		*8C*
	Number	%	*Number*	%	*Number*	%	%
Males							
15-34	2,922	30·6	1,663	32·9	4,585	31·2	27·1
35-44	1,189	12·4	861	16·7	2,050	14·0	12·6
45+	2,099	22·0	1,037	20·2	3,136	21·3	16·3
Total ..	6,210	65·0	3,561	69·8	9,771	66·5	56·0
Females							
15-34	2,265	23·7	1,054	20·6	3,319	22·7	27·1
35-44	460	4·8	275	5·4	735	5·1	6·3
45+	620	6·5	219	4·2	839	5·7	9·7
Total ..	3,345	35·0	1,548	30·2	4,893	33·5	43·1
Total							
15-34	5,187	54·3	2,717	53·5	7,904	53·9	54·2
35-44	1,649	17·2	1,136	22·1	2,785	19·1	18·9
45+	2,719	28·5	1,256	24·4	3,975	27·0	26·0
Total ..	9,555	100·0	5,109	100·0	14,664	100·0	99·1

Incidence of Tuberculosis in Persons

It will be seen from Table II that the yield in contact firm employees of cases labelled D/TO was twice (0·91 per cent.) the yield given by the routine Mass X-ray Unit (0·44 per cent.). The difference is to be seen in both males and females. It also persists after further chest clinic follow-up of these cases. For example, amongst the contact firm examinees 3·3 per thousand (48 cases) were found to have "active" tuberculosis and 0·75 per thousand (11—9 men and 2 women) were classified as infectious. On the routine unit, however, 1·6 per thousand (73) were found to have "active" tuberculosis and 0·45 per thousand (20—12 men and 8 women) were classified as infectious.

TABLE II.—NUMBERS X-RAYED BEFORE AND NOT X-RAYED BEFORE OF CONTACT FIRMS COMPARED WITH 8C EXAMINEES 1955 WITH CASES WITH RADIOLOGICALLY SIGNIFICANT LESIONS, PROBABLY TUBERCULOUS, REQUIRING INVESTIGATION

	Contact firms								
	Male			*Female*			*Total*		
	No. in Group	*No. D/TO*	*% D/TO*	*No. in Group*	*No. D/TO*	*% D/TO*	*No. in Group*	*No. D/TO*	*% D/TO*
NXR ..	4,298	51	1·19	2,195	18	0·82	6,493	69	1·06
XRB ..	5,473	51	0·93	2,698	14	0·52	8,171	65	0·79
Total ..	9,771	102	1·04	4,893	32	0·65	14,664	134	0·91

	8C Unit								
	Male			*Female*			*Total*		
	No. in Group	*No. D/TO*	*% D/TO*	*No. in Group*	*No. D/TO*	*% D/TO*	*No. in Group*	*No. D/TO*	*% D/TO*
NXR ..	5,805	54	0·93	5,774	25	0·43	11,579	79	0·68
XRB ..	18,658	82	0·44	13,370	30	0·22	32,028	112	0·35
Total ..	24,563	136	0·55	19,044	55	0·29	43,607	191	0·44

KEY: D/TO=Radiologically significant lesions, probably tuberculous, requiring supervision.
NXR=Not X-rayed before.
XRB=Examinees who have been X-rayed some time previously.

Incidence of Tuberculosis in Persons who have never previously had a Chest X-ray Examination

The incidence of tuberculosis (D/TO) in persons who had never previously had a chest X-ray examination was 1·1 per cent. in 6,493 such persons from contact firms, compared with 0·68 per cent. of 11,579 similar people from Unit 8C.

Incidence of Tuberculosis in Persons who have at some Previous Occasion undergone Chest Radiography

Table II shows that ordinary mass X-ray volunteers who *have* had a chest X-ray before contain 0·35 per cent. people found to have lesions coded D/TO, while in contact firm examinees who have had a chest X-ray before 0·8 per cent. are thus coded.

Effect of Size of Volunteer Group

The average number X-rayed at the high yield firms was 308; the average number X-rayed at low yield firms was 255. Among 19 firms in which the yield of D/TO cases was 0·5 per cent. or more, the average size was 315. Among 13 such groups in which the yield of D/TO cases was less than 0·5 per cent. the average number was 137. On 11 visits made at the request of chest physicians to firms of more than 150 volunteers at least 1 case of tuberculosis was found at every visit.

Effect of Previous X-ray on Yield of Tuberculosis

Fifty-five per cent. of contact firm examinees had already had a previous chest X-ray examination. Of all " low yield " firm employees 68 per cent. had had previous chest X-rays. Of all " high yield " firm employees only 49 per cent. had been X-rayed before, and as the yield of tuberculosis in people who had been X-rayed before was lower than in people who had not been X-rayed before (0·79 per cent. as against 1·06 per cent.), the difference between high and low yield groups is *partially* explicable on the basis of a lower proportion of

TABLE III.

	X-rayed Before High Yield Groups				*Not X-rayed Before High Yield Groups*		
	No. examined	*D/TO's*	*Rate*		*No. examined*	*D/TO's*	*Rate*
Male ..	3,055	41	1·35%	Male ..	3,155	49	1·56%
Female ..	1,631	13	0·8%	Female	1,714	18	1·05%
Total ..	4,686	54	1·15%	Total ..	4,869	67	1·37%
	Low Yield Groups				*Low Yield Groups*		
	No. examined	*D/TO's*	*Rate*		*No. examined*	*D/TO's*	*Rate*
Male ..	2,418	10	0·41%	Male ..	1,143	2	0·17%
Female ..	1,067	1	0·09%	Female	481	0	—
Total ..	3,485	11	0·31%	Total ..	1,624	2	0·12%
Total XRB	8,171	65	0·79%	Total NXR	6,493	69	1·06%

(*a*) Of all contact firm employees 55% had had previous X-ray examination.
(*b*) Of all low yield firm employees 68% had had previous X-ray examination.
(*c*) Of all high yield firm employees 49% had been X-rayed before.

X.R.B. (X-rayed before) examinees in the high yield firms than in the low yield ones. However, again the factor of previous examination will not adequately explain the difference between the high and low yield groups. For example, Table III shows that in males in the high yield group who had been X-rayed before the yield was 1·35 per cent., while in the low yield firms the significant tuberculosis rate in men also X-rayed before was only 0·41 per cent.—*i.e.*, only one-third of the rate for the comparable group in the high yield firms. More striking still is the comparison for females X-rayed before in the high yield firms where the rate is 8 times as great as in females X-rayed before in the low yield firms (Table III). The difference between high and low yield firms is not, therefore, mainly a matter of the different proportions they contain of examinees who have been previously X-rayed.

Analysis showed that in the high yield contact firms a greater proportion of examinees had either not been X-rayed before or had only been X-rayed four or more years previously, while low yield firms tend to contain people who had been examined during the preceding one to three years.

It will be helpful to recapitulate the findings given above.

The populations of firms from which new cases of tuberculosis are arising tend to have the following characteristics:

(1) Age/sex composition not different from ordinary mass X-ray examinees. (When we compare the populations of high and low yield firms we again find that they do not differ in the age/sex composition of the populations.)

(2) A higher proportion of people who have never had a chest X-ray before than ordinary mass X-ray examinees. However, this is not a complete explanation of the different yields of tuberculosis, because in every case the high incidence of tuberculosis in contact firm examinees persists even when the groups are so analysed that these differences are eliminated—for example, the incidence of tuberculosis in contact firm examinees who have never previously had a chest X-ray is much higher than in ordinary mass X-ray examinees who have never had a chest X-ray before.

Investigation into Possible Reasons for High Incidence of Tuberculosis in Contact Firm Examinees

(1) No estimates of socio-economic status of contact firm examinees compared with employees of firms examined by routine mass radiography has been possible, but with a few exceptions, there is nothing (*e.g.*, poverty, poor working conditions) obviously to differentiate the contact firm from any other when one visits the premises.

(2) The works contact firms with their higher proportion of examinees who have never previously been X-rayed are probably those that have not been visited by mass X-ray units. It seems, then, that cases of tuberculosis now coming to the clinics are " arising " largely in firms which have escaped the mass X-ray net. However, the high proportion of N.X.R. (never X-rayed before) examinees in these firms is *not* a complete explanation of the high yield in those firms, because contact firm N.X.R. (not X-rayed before individuals) examinees have much more tuberculosis than N.X.R. examinees from non-contact firms.

(3) Could it be the case that the risk of contracting tuberculosis in a firm is related to the proportion of people in that firm who have not been previously X-rayed? To test this hypothesis the firms were divided up according to the proportion of their staff who had never been previously X-rayed (Table IV). We then found the incidence of tuberculosis in these groups of firms among examinees who had never been previously X-rayed (excluding all previously X-rayed examinees of the same firms and cases of tuberculosis discovered in the survey who had been previously X-rayed). Table IV shows that it is more "dangerous" to be a "not examined" person surrounded by a majority of others who have *not* been examined, than to be a "not examined" person surrounded by others the majority of whom *have* had a previous chest X-ray. The findings suggest that not only does previous X-ray examination "protect" the person who has been X-rayed, but that those who have never been examined are also enjoying a lower incidence of tuberculosis when most of their fellows have come forward for examination. That is, they suggest a "protective" effect of mass radiography even on the un-X-rayed members of the population.

TABLE IV.—TABLE SHOWING RELATIONSHIP BETWEEN PERCENTAGE NXR* IN GROUPS OF FIRMS AND YIELD OF RADIOLOGICALLY SIGNIFICANT LESIONS, PROBABLY TUBERCULOUS, REQUIRING SUPERVISION IN NXR* EXAMINEES

% *NXR* in firms*	*Number NXR**	*Number D/TO's in NXR's*	% *D/TO's in NXR's*
0-30	1,409	11	·78
31-59	6,247	63	1·01
60+	3,088	41	1·33
Total NXR examinees	10,744	115	1·07

* Not X-rayed before.

N.B.—In this table the number of employees has been increased by 4,316 by including results of surveys carried out up to August 1956.

Summary

1. Mass X-ray surveys were made of the staffs of 51 firms in which a case of tuberculosis had "recently occurred."

2. The 134 cases of tuberculosis significant for chest clinic supervision were found among 14,664 people examined in the contact guided surveys (0·91 per cent.). This rate of yield was twice the rate found in comparable routine mass X-ray surveys (0·44 per cent.).

3. The age/sex composition of the contact firms' staffs did not differ from the populations examined by ordinary mass radiography, but they contained a greater proportion of people who had never had a chest X-ray before.

4. The excess of people never X-rayed before in contact firms' staffs partly, but not mainly, accounts for the excess of tuberculosis cases found on these visits.

5. The incidence of tuberculosis *among examinees never* X-rayed before varies from firm to firm according to the proportion the firm contains of people who

have been previously X-rayed. These findings suggest that Mass Radiography has not only a " protective " effect on those who volunteer, but that it also has a protective effect on those who, although they do not themselves volunteer, are surrounded by people who have been X-rayed.

This work could not have been carried out without the co-operation of a number of people to whom gratitude is due, especially Dr. P. C. Anderson, Dr. G. C. Taylor, Dr. J. G. Tomkins, Mr. William Merson, M.S.R., Miss Vera Farrow, Miss Joyce Strudwick and the staff of the South-west London Mass X-ray Service. Thanks are also due to the following Chest Physicians and their staffs: Dr. J. R. Bignall, Dr. R. H. J. Fanthorpe, Dr. H. F. Harwood, Dr. J. M. Hill, Dr. J. J. MacDonnell, Dr. J. G. S. McQueen, Dr. H. J. Partington, Dr. H. C. Price, Dr. E. Sanders, Dr. I. S. Thomson, Dr. F. J. H. Walters.

I am grateful to the South-west Metropolitan Regional Hospital Board for authorising the provision of the necessary staff and equipment from research funds.

PYRAZINAMIDE TOGETHER WITH OXYTETRACYCLINE IN PATIENTS WITH TUBERCLE BACILLI RESISTANT TO STREPTOMYCIN, PAS AND ISONIAZID

By Sheila M. Stewart,* J. McC. Murdoch, J. W. Crofton and David Hay

From the Department of Tuberculosis and Diseases of the Respiratory System, University of Edinburgh

Medical Research Council trials have established combinations of streptomycin, PAS (para-aminosalicylic acid) and isoniazid which in our experience almost completely avoid the emergence of drug-resistant organisms in pulmonary tuberculosis, however prolonged the treatment (Medical Research Council, 1953a, b). Unfortunately there are a number of patients whose bacilli have become resistant to two or more of these drugs owing to previous treatment with drug combinations now known to be unsatisfactory. The use of isoniazid *plus* oxytetracycline (terramycin) in patients whose bacilli are resistant to streptomycin and PAS has already been described (Stewart *et al.*, 1954). We have also reported experience with viomycin *plus* oxytetracycline in patients whose bacilli were resistant to streptomycin, PAS and isoniazid (Murdoch and Stewart, 1955). This latter combination is a weak one and did not achieve a great deal in the far advanced chronic cases admitted to the trial. It was therefore desirable to find a more effective alternative. In the United States pyrazinamide has been found to be an effective drug over a short period (Yeager *et al.*, 1952), the limitation of its action probably being due to drug resistance. In the present trial, an attempt was made to delay pyrazinamide resistance by giving oxytetracycline at the same time.

Material

It was thought that, as there were relatively few suitable patients, a careful serial assessment of the number of bacilli in the sputum would be the most sensitive way of estimating the value of the drug combination. Accordingly, patients were only admitted to the trial if three successive sputa were positive on direct smear. All but one of the cases had been in hospital for at least twelve months and the sputum of all had been consistently positive for at least fifteen months. The known duration of illness ranged from two and a half to fifteen years. All but two of the patients (cases 6 and 11) had had previous courses of oxytetracycline in conjunction with antituberculous drugs for periods of three to twenty-five months. In a series of eighty patients treated with such combinations, often for many months, we have never encountered resistance to oxytetracycline. All the present series had bacilli sensitive to this drug at the start of treatment.

* Royal Victoria Hospital Tuberculosis Trust Research Fellow in Bacteriology.

(*Received for publication December* 21, 1956.)

All patients had bilateral disease and extensive cavitation and only one was fit for surgery. They were the hard core of a group who had initially received unsatisfactory chemotherapy resulting in the emergence of resistant organisms, and whom it had not previously been possible to salvage by other forms of chemotherapy or by surgery.

Eleven cases were admitted to the trial. In Table 1 are given details of their disease before the start of pyrazinamide *plus* oxytetracycline.

TABLE I.—CLINICAL CONDITION OF THE PATIENTS PRE-TREATMENT

Case No.	*Age*	*Sex*	*Known length of illness (years)*	*Duration in hospital (months)*	*Sputum volume in 24 hrs. (ml.)*	*Total diameter of cavities (cm.)*
1	30	M	10	1	340	23·0
2	54	M	7	12	40	10·0
3	41	M	7	72	60	17·0
4	49	M	2½	24	50	17·5
5	24	F	10	51	70	17·0
6	49	M	15	54	170	3·0
7	40	M	6	54	480	21·0
8	30	F	5	12	30	18·0
9	32	F	5	51	15	21·0
10	43	M	5	18	75	14·0
11	50	F	6	22	70	14·0

METHODS

Pyrazinamide was given in a dose of 40 mg. per kg. of body weight per day in two divided doses. Ten of the eleven patients received oxytetracycline in a dose of 2 g. twice daily. In the eleventh (case 8) the dose was reduced to 1 g. twice daily after the first month owing to nausea and vomiting. All patients were treated for at least three months.

Bacteriological methods:

Assessment of the number of bacteria in the sputum was made by four different methods:

(1) A comparison of a direct smear of the test sputum with standard smears.

An equal volume of sterile distilled water was added to the sputum and it was shaken mechanically with glass beads for 15 minutes. A standard 3 mm. loopful of the homogenate was then smeared on to a slide to cover an area of 1×2 cm. The film was fixed and stained by the Ziehl-Neelsen method. The degree of positivity was graded by comparison with two standard smears, standard smear 1 having approximately 5 bacilli per $\frac{1}{12}$ in. oil immersion field and standard smear 2 approximately 1 bacillus per 5 fields. The results were expressed as follows:

+++=More positive than standard smear 1.
++=Less positive than standard smear 1, but more positive than 2.
+=Less positive than standard smear 2.

(2) A count of the number of bacilli on the concentrate film.

After concentration by the alkali-acid technique and washing with sterile distilled water, the sputum was re-centrifuged at 2,500 revolutions per minute. From the resulting deposit a concentrate film was made by smearing a standard 3 mm. loopful over an area of 1×2 cm. After staining by Ziehl-Neelsen, the total number of bacilli in twenty $\frac{1}{12}$ in. oil immersion fields was counted. From this figure the average number of organisms per field was calculated.

(3) A count of the number of viable organisms.

After the concentration, washing and re-centrifuging of the sputum, the deposit was suspended in 0·4 ml. sterile distilled water and shaken mechanically for 15 minutes. From the resulting suspension tenfold serial dilutions were prepared in distilled water. Four consecutive dilutions were inoculated on to the four quadrants of two Löwenstein-Jensen plates which had been dried at 37° C. before use. The plates were left on the bench overnight. They were then inverted and wax run into the rim to prevent evaporation. The plates were incubated at 37° C. for six weeks. Colony counts were made and the number of viable bacilli per ml. of concentrate calculated. If there was a discrepancy between the two counts, the average was taken.

(4) Quantitative grading of the cultures.

One Löwenstein-Jensen slope in a 1 oz. (28 ml.) McCartney bottle was inoculated with 0·2 ml. of the sputum concentrate. The slope was laid down overnight and then placed in the incubator in the upright position. The amount of growth on the slope was graded as follows:

+++ = Confluent growth over the whole slope.
++ = Innumerable discrete colonies.
+ = 20 to 100 colonies.

Where less than 20 colonies were present, the exact number was reported.

Methods (1) and (4) were based on those devised by the Bacteriological Subcommittee of the Medical Research Council of Great Britain (1955).

The assessments were carried out twice weekly for the first two months and weekly thereafter. Two estimates were made during the week before the start of treatment.

Resistance tests to pyrazinamide and oxytetracycline were carried out monthly. The following techniques were used:

Pyrazinamide: Pyrazinamide sensitivity tests were carried out in Dubos and Davis liquid medium without the addition of " Tween 80 " at a *p*H of 6·0 by a method based on that reported by McDermott and Tompsett (1954). (In some later batches medium at *p*H 5·8 was used.) The growth from the primary culture on Löwenstein-Jensen medium was inoculated into Dubos and Davis medium containing " Tween 80 " at *p*H 7·0. After ten days' incubation, a sub-culture was made into liquid medium with " Tween 80 " at *p*H 6·0 in order to adapt the organisms to growth at the lower *p*H and yet give an even culture for the inoculation of the drug-containing medium. 0·02 ml. of this second sub-culture was inoculated into 3·0 ml. quantities of the drug-medium mixture. The actual

concentrations of the drug in the medium were 2,000 μg. per ml. by twofold dilutions to 15·0 μg. per ml. The results were expressed as a resistance ratio—that is, the ratio of the minimum concentration of the drug inhibiting the growth of the test organism to that inhibiting the growth of the standard sensitive strain H 37 Rv. The standard strain was normally inhibited by 31 to 125 μg. pyrazinamide per ml.

Some batches of tests had to be discarded owing to the growth of the sensitive strain at concentrations of the drug above 250 μg. per ml. This occurred only occasionally when the tests were carried out in medium at *p*H 5·8.

Organisms were considered to be resistant to pyrazinamide if the resistance ratio was eight or over.

Oxytetracycline: Oxytetracycline resistance tests were carried out by the method already reported using Dubos and Davis medium at *p*H 7·0 (Stewart *et al.*, 1954). The actual concentrations of the drug in the medium were 64 μg. per ml. by twofold dilutions to 1 μg. per ml. The results were reported as resistance ratios. The standard H 37 Rv strain was normally inhibited by 2 or 4 μg. oxytetracycline per ml.

Isoniazid: Isoniazid resistance tests were carried out on pre- and post-treatment cultures by the method recommended by the Medical Research Council of Great Britain (1953c) using Löwenstein-Jensen medium. The isoniazid concentrations used were 50, 10, 5, 1 and 0·2 μg. per ml. The results were expressed as the highest concentration allowing the growth of 20 or more colonies.

Clinical assessment:

The patient's general condition, sputum volume, weight and erythrocyte sedimentation rate (E.S.R.) were recorded each month. Radiographs were taken monthly and were assessed by an independent panel unaware of the treatment given. Other trials were running concurrently and the cases were mixed at random for the panel readings. At each assessment all the films were re-read without knowledge of the previous conclusions, thus providing a check on the readings. The occasional differences in interpretation were discussed and agreement reached on a final result.

Toxicity Studies:

In view of previous reports of a toxic effect of pyrazinamide on the liver, the urine was examined weekly for excess of urobilinogen and estimations were made fortnightly of serum bilirubin, thymol turbidity and alkaline phosphatase.

Results

Although not entirely uniform, the results were surprisingly consistent for such a variable disease as pulmonary tuberculosis. This was probably because all the patients had extensive chronic cavities and very large bacillary populations. Only a powerful combination of drugs capable of acting for a long time without the emergence of resistant organisms would be likely to achieve sputum conversion in such cases.

Bacteriological results:

Except for one case whose initial bacterial count was very large (case 5), all cases showed a marked drop in count by one or more methods of estimation in the first fourteen to forty days of treatment. Subsequently there was an equally steady rise with the emergence of pyrazinamide-resistant organisms. In Table II are given the two pre-treatment viable counts for each patient, the day of

TABLE II.—THE NUMBER OF VIABLE BACILLI PRESENT IN THE SPUTUM BEFORE AND DURING TREATMENT

Case No.	*Pre-treatment counts (per ml.)*		*Lowest count (per ml.)*	*Treatment day with lowest count*	*First appearance of resistance (days)*	*"Plateau" count**	*Treatment day when "plateau" reached**
	1	2					
1	$7{\cdot}2\times10^{5}$	$2{\cdot}5\times10^{4}$	$1{\cdot}0\times10^{4}$	17	63	$7{\cdot}5\times10^{5}$	45
2	$4{\cdot}8\times10^{4}$	$1{\cdot}2\times10^{6}$	0	31	38	$1{\cdot}6\times10^{5}$	70
3	$1{\cdot}5\times10^{4}$	$4{\cdot}0\times10^{3}$	0	14	77	$2{\cdot}0\times10^{4}$	91
4	$7{\cdot}5\times10^{5}$	$2{\cdot}8\times10^{5}$	$4{\cdot}0\times10^{3}$	18	28	$>2{\cdot}5\times10^{6}$	46
5	$>2{\cdot}5\times10^{6}$	$>2{\cdot}5\times10^{6}$	No fall		52	—	—
6	$5{\cdot}5\times10^{3}$	$1{\cdot}1\times10^{3}$	0	40	60	$3{\cdot}0\times10^{5}$	85
7	$2{\cdot}5\times10^{6}$	contam.	$5{\cdot}0\times10^{3}$	20	61	$7{\cdot}5\times10^{5}$	54
8	$6{\cdot}5\times10^{7}$	$1{\cdot}4\times10^{7}$	$4{\cdot}8\times10^{3}$	14	45	$2{\cdot}5\times10^{6}$	52
9	$2{\cdot}8\times10^{6}$	$3{\cdot}5\times10^{6}$	$1{\cdot}5\times10^{4}$	28	84	$1{\cdot}0\times10^{6}$	56
10	$1{\cdot}7\times10^{6}$	$3{\cdot}5\times10^{6}$	$2{\cdot}0\times10^{3}$	30	53	$1{\cdot}5\times10^{5}$	106
11†	$3{\cdot}0\times10^{5}$	$2{\cdot}5\times10^{6}$	$5{\cdot}0\times10^{2}$	31	59	$4{\cdot}0\times10^{4}$	52

* For explanation see text.

† This patient had a left thoracoplasty one day after starting treatment and a left upper lobectomy 42 days later.

treatment when the lowest count was obtained, the figure for the lowest count and the day of treatment when the graph showed that the count had returned to the original plateau. Two typical graphs, showing the consistency of the different methods within the usual wide range of biological error, are given in Fig. I. The graphs in the other patients who showed a drop in count were similar, but space does not permit of their reproduction. Because of toxic symptoms (see below) one patient (case 10) had his treatment interrupted for twenty days. Allowing for this, the graph was very similar to the others.

Drug resistance to pyrazinamide:

The estimation of resistance of tubercle bacilli to pyrazinamide has been difficult owing to the low *in vitro* activity for most organisms at neutral *p*H. Some batches of tests had to be discarded owing to the growth of the sensitive strains at high concentrations of the drug. Owing to the variability of the minimum inhibitory concentrations for such strains, the results have always been reported as resistance ratios.

From Table III it will be seen that resistant organisms were isolated in all cases after periods of treatment varying from twenty-eight to eighty-four days. The emergence of these bacilli was related to the increase in sputum positivity which occurred in the ten cases who had had an initial drop during the first month.

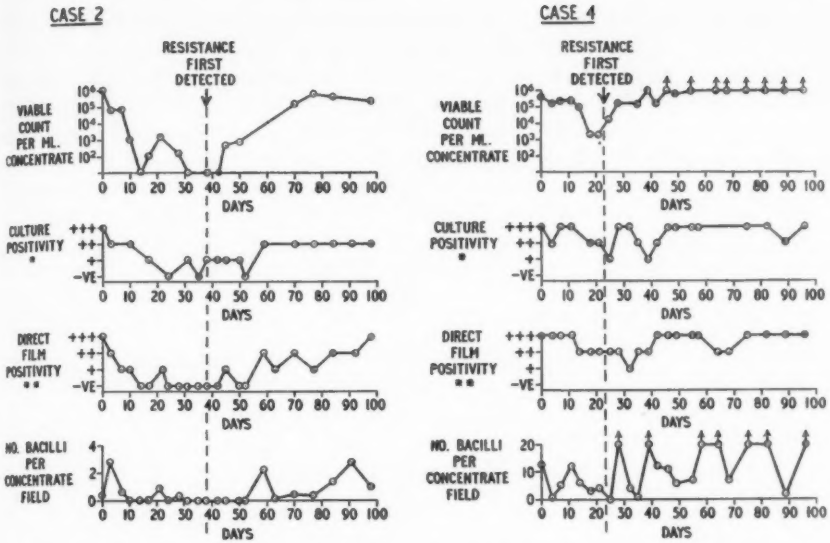

FIG. 1.—Graphs of serial readings of the degree of positivity of the sputum of two cases during the first 100 days of treatment with pyrazinamide and oxytetracycline.
The intermittent vertical line indicates the time at which resistant organisms were first isolated.

* Culture positivity:

+++ = Confluent growth over whole slope.
++ = Innumerable discrete colonies.
+ = 20 to 100 colonies.

** Direct film positivity:

+++ = More positive than standard smear 1.
++ = Less positive than standard smear 1, but more positive than smear 2.
+ = Less positive than standard smear 2.

In all but one of the cases the organisms were at least thirty-two times as resistant to pyrazinamide as the test strain. In the eleventh case, the resistance ratio was greater than eight. So far no results are available on cultures obtained after the end of treatment. It is therefore not yet known whether this resistance is permanent.

Clinical Results:

On the whole the clinical results tended to follow the bacteriological state, although as might be expected in this type of case there was little radiological change. The data are summarised in Table IV for cases 1 to 10. In the eleventh case, thoracoplasty and left upper lobectomy were performed within two months of the start of treatment. It was therefore not possible in this case to assess whether the clinical changes were due to pyrazinamide therapy or to surgery.

Improvement during the first one to two months of treatment occurred in the general condition of four patients and in the radiographs of two cases. In

TABLE III.—THE RESULTS OF PYRAZINAMIDE RESISTANCE TESTS AT MONTHLY INTERVALS DURING TREATMENT

The figures indicate resistance ratios, that is, the minimum inhibitory concentration for the test strain to the minimum inhibitory concentration for the standard H37Rv strain.

Case No.	*Pyrazinamide resistance as resistance ratio—after months of treatment*			*First appearance of resistance*
	1	2	3	
1	2	>32	>8	63
2	16	32	>8	38
3	Culture -ve.	>8	>8	77
4	> 32	>32	>8	28
5	1	>64	>4	52
6	4	>64	>8	60
7	1	>64	>4	61
8	1/2	>4	>32	45
9	1/2	2	64	84
10	2	>64	>8	53
11*	1/2	32	>4	59

* Bacilli isolated from the lung specimen of this patient obtained 43 days after the start of treatment had a resistance ratio of >32.

TABLE IV.—CLINICAL PROGRESS UNDER TREATMENT
(10 cases—excludes case 11: operation)

	Grading	*Pre-treatment*	*After treatment**		
			1 month	*2 months*	*3 months*
General condition ..	Improved		4	1	0
	No change		6	7	8
	Deteriorated		0	2	2
Radiological improvement	Improved		1	1	0
	No change		9	8	7
	Deteriorated		0	1	3
Sputum volume (mls.) ..	Decreased		4	0	0
	No change		5	7	6
	Increased		1	3	4
	Average	133·0	96·0	124·5	153·5
Weight (lbs.)†	Increased		4	1	2
	No change		3	2	5
	Decreased		2	6	2
	Average	103	104	102	101

* The comparisons are between successive months.
† One patient was too ill to weigh throughout.

four of the cases there was a marked reduction of the twenty-four-hour sputum volume. Excluding the patient who was operated upon, eight out of the ten patients improved by at least one of these criteria. Eight of the ten cases showed deterioration after the emergence of resistant organisms. One patient (case 7) died four and a half months after starting treatment.

One case (case 11), mentioned above, had a left thoracoplasty the day after starting treatment and a left upper lobectomy forty-two days later. A reduction in sputum positivity occurred between the two operations, but the sputum was again strongly positive before the lobectomy was performed. Pyrazinamide-resistant organisms were isolated from the lung specimen and from the sputum.

Toxicity:

Only two patients showed any signs of toxicity to the drugs. One of these (case 8) had marked nausea and vomiting during the first month when she was receiving 2 g. oxytetracycline twice daily. However, when the dose was reduced to 1 g. twice daily, the drug was well tolerated. The second patient also complained of nausea and refused to take the drugs after one month of treatment. The drugs were, however, re-started three weeks later in a disguised form with no further symptoms.

Isoniazid resistance:

In five cases (cases 1, 4, 6, 7 and 9) the bacilli were resistant to 50 μg. isoniazid per ml. of Löwenstein-Jensen medium before the start of pyrazinamide treatment. In three (cases 5, 8 and 11) the organisms were resistant to 1 μg. per ml. and in one (case 3) to 0·2 μg. per ml. In the remaining two cases (cases 2 and 10) the bacilli had reverted to complete sensitivity, having at some time previously been resistant to 50 μg. per ml. In none of the cases was any alteration in the degree of isoniazid resistance observed during the period of treatment with pyrazinamide. There was no correlation between the degree of isoniazid resistance pre-treatment and the clinical and bacteriological response to therapy.

Discussion

It is possible to obtain valuable information about new drugs by a trial on a relatively small number of patients provided that these have chronic disease, extensive cavitation and sputum consistently positive on direct smear. Preferably the patients should have already experienced maximal benefit from bed-rest. Of course, trial of a new drug is only justified if the patient's bacilli are already resistant to streptomycin, PAS and isoniazid. It is possible by detailed study of such cases to determine whether a drug is having an effect and whether it is worth investigating on a wider scale. In this type of patient assessment is little affected by the natural improvement which may occur in those with milder or less extensive disease, and control cases are less important. In addition, the chances of drug resistant bacilli emerging are maximal, so that this vital aspect can be assessed. Admittedly these conditions set any new drug a formidable task, but in general any new drug or drug combination has to stand comparison with streptomycin *plus* isoniazid, which is effective even in this type of case (Douglas and Horne, 1956). Screening of this kind may provide valuable

information, avoiding waste of time on the more extensive controlled trials should the results prove negative.

In the present limited trial it has been established, in agreement with less detailed work in the United States (Yeager *et al.*, 1952), that pyrazinamide has an important, in some cases dramatic, effect on the tubercle bacillus *in vivo* in man. Also in accordance with previous work, we have found that this effect is of relatively short duration. Clinically patients began to " escape " from the effect in the second month of treatment. This was paralleled by a steep rise in the degree of sputum positivity about the fortieth day in the ten cases in whom there had been an initial drop. We have shown that their " escape " was associated with the emergence of bacilli resistant to pyrazinamide. There was little evidence that oxytetracycline, even in the large doses given, had any effect in delaying the emergence of pyrazinamide-resistant bacilli. Nevertheless, in the absence of a control group on pyrazinamide alone, we cannot exclude the possibility that oxytetracycline had some slight effect. Although we expected trouble from the toxic effects of pyrazinamide, especially in advanced cases, this did not prove a problem.

Would any drug be more effective in delaying resistance and in maintaining the powerful antibacillary effect of pyrazinamide? Schwartz and Moyer (1954) think that neither streptomycin nor PAS is effective in preventing pyrazinamide resistance as judged clinically. At that time it had not been found feasible to carry out resistance tests *in vitro*.

On the other hand, it has been claimed, on the basis of experimental work in mice, that pyrazinamide *plus* isoniazid is a very powerful combination (McDermott *et al.*, 1954; Schwartz and Moyer, 1954; Phillips and Horton, 1956). In the United States Veterans Administration controlled trials, Livings (1956) found that pyrazinamide *plus* isoniazid was at least as good and probably better than daily PAS *plus* isoniazid and also than intermittent streptomycin combined with either isoniazid or PAS daily. Phillips (1956) found that pyrazinamide *plus* isoniazid was roughly equivalent to PAS *plus* isoniazid. Both these workers record a number of cases of liver damage due to pyrazinamide. This, though it has not so far occurred in our cases, is generally regarded as a major disadvantage of the drug.

Until a drug can be found which will prevent pyrazinamide resistance more effectively than oxytetracycline, it is probably wise in patients whose bacilli are resistant to streptomycin, PAS and isoniazid to use the drug only for covering operations. It is unlikely to be effective for more than four to six weeks, but it may greatly improve the patient's condition during the early part of that time. Unfortunately many of the patients in question need much longer preparation for operation. It is possible that some may be prepared by prolonged viomycin *plus* oxytetracycline, weak though this combination is, pyrazinamide being substituted or added over the operation period. In our view there is at present no place for pyrazinamide in the routine treatment of patients whose organisms are sensitive to streptomycin, PAS and isoniazid. But its value, combined with isoniazid, in patients with streptomycin- and PAS-resistant bacilli, needs to be further assessed. It may be more effective than oxytetracyline in preventing the emergence of isoniazid-resistant organisms.

Summary

Eleven cases of far-advanced cavitated pulmonary tuberculosis, with organisms resistant to streptomycin, PAS and isoniazid, were treated with pyrazinamide *plus* oxytetracycline for at least three months.

There was a fall in sputum positivity in ten of the cases with a subsequent rise in positivity coinciding with the emergence of pyrazinamide-resistant bacilli. No oxytetracycline resistance was encountered.

Clinically there was some improvement in most of the cases, but there tended to be an " escape " from the effect of the drug in the second month of therapy after the emergence of drug-resistant organisms.

No toxic effects attributable to pyrazinamide were noted.

Oxytetracycline probably does not appreciably delay the onset of pyrazinamide resistance or prolong the short effectiveness of the drug when given alone.

This investigation was carried out on behalf of Drs. I. W. B. Grant, N. W. Horne and J. D. Ross, who were in clinical charge of the patients.

We are indebted to the nursing and laboratory staffs of the City Hospital, Edinburgh, and East Fortune Hospital, Drem, for assistance in the collection of the specimens.

The work was supported by a generous grant from the Royal Victoria Hospital Tuberculosis Trust.

Pyrazinamide was kindly supplied, through the courtesy of Dr. Richard Bayliss, by Messrs. Merck Sharp and Dohme Ltd.

REFERENCES

Douglas, A. C., and Horne, N. W. (1956): *Brit. med. J.*, **1**, 375.

Livings, Dorothy G. (1956): Transactions of the 15th Conference on the Chemotherapy of Tuberculosis, U.S. Veterans Administration, Army and Navy, p. 101.

McDermott, W., and Tompsett, R. (1954): *Amer. Rev. Tuberc.*, **70**, 748.

McDermott, W., Ormond, L., Muschenheim, C., Deuschle, K., McCune, R. M. Jr., and Tompsett, R. (1954): *Amer. Rev. Tuberc.*, **69**, 319.

Medical Research Council (1953a): *Brit. med. J.*, **1**, 521.

(1953b): *Brit. med. J.*, **2**, 1005.

(1953c): *Lancet*, **2**, 213.

(1955): Personal communication.

Murdoch, J. McC., and Stewart, Sheila M. (1956): *Brit. J. Tuberc. Dis. Chest*, **50**, 85.

Phillips, S. (1956): Transactions of the 15th Conference on the Chemotherapy of Tuberculosis, U.S. Veterans Administration, Army and Navy, p. 112.

Phillips, S., and Horton, G. E. (1956): *Amer. Rev. Tuberc.*, **73**, 704.

Schwartz, W. S., and Moyer, R. E. (1954): *Amer. Rev. Tuberc.*, **70**, 413.

Stewart, Sheila M., Turnbull, F. W. A., and Crofton, J. W. (1954): *Brit. med. J.*, **2**, 1508.

Yeager, R. L., Munroe, W. G. C., and Dessau, F. I. (1952): *Amer. Rev. Tuberc.*, **65**, 523.

VIOMYCIN AS OPERATIVE COVER FOR MAJOR SURGERY FOR PULMONARY TUBERCULOSIS

By J. R. Edge, M. Kamiel, N. C. Scott and J. C. P. Weber

High Carley Hospital, Ulverston

Experimental evidence that Viomycin, an antibiotic prepared from *Streptomyces Floridæ*, is effective against *M. tuberculosis in vitro* and in animal experiment was presented by Finlay *et al.*, Bartz *et al.*, Ehrlich *et al.*, Hobby *et al.*, Youmans and Youmans, Steenken and Wolinsky, Karlson and Gainer, P'an *et al.* (1951). At the same time Werner *et al.* described numerous toxic effects (renal irritation, serum electrolyte disturbance, eighth nerve lesions and hypersensitivity reactions) in ten far advanced patients treated with a large daily dose over a period of from two to twenty-nine weeks (30-75 mg./kg.). Pitts *et al.* (1953) and Schaffeld *et al.* (1954) describe an encouraging clinical response, though distinctly smaller than to streptomycin. Using an intermittent régime they found a substantial but in no way prohibitive incidence of toxic effects. Adcock *et al.* (1954), describing a similar experience, remarks that " there will be fewer patients in whom this drug is indicated since the advent of Isoniazid, but situations will continue to arise in which it should be used."

Viomycin only became freely available in this country in 1954. Murdoch and Stewart (1956), describing their experience in the use of oxytetracycline in preventing the emergence of Viomycin-resistant strains, conclude that these drugs may permit of major surgery in patients with otherwise hopeless disease, but believe that they should be reserved for cases in which no other effective chemotherapy is available.

Present Material

This paper concerns thirty-six consecutive patients admitted to hospital for major surgery, who were found to carry organisms moderately or completely resistant* to at least two of the three standard anti-tuberculous agents. All had had considerable periods of antibacterial treatment before admission, in spite of which they remained sputum positive; using the classification recommended by Foster Carter *et al.* (1952),† two patients fell into Class I, seven into Class II, whilst twenty-seven were in Class III. Twenty-five were submitted to resection,

* Partial resistance indicates growth in 1 microgramme of Isoniazid, 3 microgrammes of Streptomycin, or 2 microgrammes of Para-aminosalicylic acid per ml. Total resistance indicates growth in 50 microgrammes of Isoniazid, 30 microgrammes of Streptomycin, or 100 microgrammes of Para-aminosalicylic acid per ml.

† Class I comprises patients with not more than one zone in one lung involved. Class II includes those patients with unilateral or bilateral disease involving two or three zones. Class III covers patients with bilateral disease affecting four or more zones.

(*Received for publication January* 31, 1957.)

and a further eleven to thoracoplasty (see table) under cover of Viomycin in combination with whatever other agent or agents appeared most suitable.

It is widely recognised that the risk of broncho-pleural fistula following resection is much increased in the presence of bacterial resistance (Bell, 1956), and Viomycin was used in this group in the hope of avoiding this or other complications over the operative period. Thoracoplasty was used for patients with extensive and bilateral disease, who were considered unsuitable for resection, with the aim of controlling the principal cavitary lesion.

Types of operation

Pneumonectomy	13
Lobectomy	5
Lobectomy plus wedge ..	2*
Segmental resection ..	5
Thoracoplasty	11
Total	36

Representative Case Histories

Case 1. M.B., a trainee nurse aged 21, was X-rayed in May 1955 because of symptoms, when a large thick-walled cavity was seen in the right upper lobe; the sputum was positive direct. Treatment with daily streptomycin (1 G.) and isoniazid (200 mg.) was started, but shortly after admission to hospital on 15.8.55 the cavity enlarged, with a bronchogenic spread to the right mid-zone. Cultures set up after only ten weeks' antibacterial treatment grew organisms resistant to 30 micrograms of streptomycin, 50 micrograms of isoniazid, and 10 micrograms of PAS per ml. She had evidently been infected with a primarily drug-resistant organism. Following Viomycin 2 G. twice weekly, with PAS 15 G. daily and isoniazid 200 mg. daily, some radiological clearing occurred and the cavity blocked; right upper lobectomy was carried out on 23.1.56 and her subsequent course was uneventful, the sputum remaining consistently negative. The same antibacterial treatment was continued until her discharge from hospital six months after operation.

Case 2. C.S., aged 38, was diagnosed in 1953, with cavitary disease in the left upper lobe. She was treated with several short courses of the standard antibacterial agents, and shortly before admission to hospital on 14.5.56 had deteriorated under treatment with PAS and isoniazid; organisms cultured from the sputum were then found to grow in 30 micrograms streptomycin, 50 micrograms of isoniazid, and 2 micrograms of PAS per ml. Viomycin 2 G. twice weekly, with PAS 15 G. daily, was started on 31.7.56 and the left upper lobe was removed on 20.8.56, together with wedge resection of a caseous lesion in the lower lobe apex; a four-rib tailoring thoracoplasty was done at the same operation. Her post-operative course was quite uneventful and she remains consistently sputum negative. Viomycin and PAS were continued until her transfer to a hospital near her home on 18.10.56.

Case 3. I.F., aged 30, was diagnosed in 1947 with cavitary disease in the right upper lobe, which was unsuccessfully treated by right artificial pneumothorax, followed in turn by an extra-pleural pneumothorax, right extra-periosteal plombage, and removal of the polythene pack with right thoracoplasty (1950). She remained consistently sputum positive, with a persisting

* One patient also had a segmental resection on the other side later, again under Viomycin.

cavity in the right upper lobe, and had several courses of antibacterial treatment. On admission to hospital the organisms were found to grow in 30 micrograms of streptomycin, 50 micrograms of isoniazid, and 100 micrograms of PAS per ml. Viomycin 2 G. twice weekly was started on 28.2.56 with Dipasic 700 mg. daily; the right upper lobe was removed on 11.4.56. The cavity was accidentally opened at operation with contamination of the pleura, but the post-operative course was quite uneventful and she has since remained sputum negative. Antibacterial treatment was continued on the same lines until her discharge from hospital six months after operation.

Case 4. S.R., aged 51, was originally diagnosed in 1949, when he had cavitary tuberculosis affecting the left lower lobe, which was resected in December 1951. Subsequently he developed a spread of disease in both lungs, and by September 1954 had extensive disease throughout the left upper lobe. After admission on 17.4.56 his organisms were found to grow in 30 micrograms of streptomycin per ml., 50 micrograms of isoniazid per ml., but not in 2 micrograms of PAS. He was quite unable to tolerate PAS, and commenced Viomycin 2 G. twice weekly, with Dipasic 600 mg. daily, on 18.4.56, which were continued until his discharge. The left upper lobe was resected on 28.5.56. His post-operative convalescence was satisfactory and he was discharged home, consistently culture negative, on 7.11.56.

Duration of Treatment

The duration of treatment with Viomycin ranged from five weeks to sixty-one weeks, with an average of twenty-three weeks; seven patients continue treatment at the time of writing. The dosage used was 2 G. (one G. morning and evening) twice weekly except in three patients, whose dosage was reduced to 1 G. twice weekly because of side-effects.

Toxic Effects

Kidneys. The urine was tested in the ward at weekly intervals, and microscopy was done if albuminuria was noted. Several patients had transient slight albuminuria with a few granular casts, which in all cases disappeared on cessation of therapy. No patient required to stop treatment because of renal disturbance.

Eighth cranial nerve. One patient complained of dizziness on 2 G. Viomycin twice weekly, which disappeared on reduction of dose to 1 G. twice weekly. No clinical evidence of deafness occurred in any patient.

Electrolyte disturbances. No clinical indication of serum sodium, potassium, or calcium disturbance was found, and routine investigation was not carried out.

There were no obvious hepato-toxic effects.

Allergy

The principal side-effects presented as rash and bronchospasm with eosinophilia, occurring immediately after the injections. Significant eosinophilia without symptoms occurred in a number of patients and was disregarded.

The drug was discontinued in one patient because of severe bronchospasm and in another because of generalised erythema with facial œdema. One patient

with severe rash, vomiting, facial œdema and fever was controlled by ACTH (Houghton, 1954) and continued treatment uneventfully.

In one patient bronchospasm ceased on reduction of dosage to 1 G. twice weekly; and a further patient who had severe conjunctivitis after 2 G. had no further trouble on reduction to 1 G. twice weekly.

Post-operative Complications

Resection

One patient developed contralateral spread of disease, and remained culture positive though clinically well six months after operation. One patient had a residual air space following segmental resection, evidently due to alveolar air leak, which had completely closed two months post-operatively. Bronchopleural fistula did not occur.

The only instance of wound infection was in a patient who had a left pleuro-pneumonectomy for a destroyed lung with chronic empyema, bronchopleural fistula and cutaneous fistula of many years' standing. She developed a tuberculous infection of part of the wound, but healing was complete six months after operation.

One patient had transient basal atelectasis.

The remaining patients pursued a quite uneventful post-operative convalescence.

Thoracoplasty

None of the eleven patients developed bronchogenic spread, Semb's space infection, wound infection or post-operative atelectasis.

Sputum Conversion

Resection

One patient (mentioned under complications) remained culture positive six months after operation, following a post-operative bronchogenic spread; and one further patient remained culture positive at six months after pneumonectomy from a pre-existing contralateral focus.

The remaining twenty-three patients were consistently negative until discharge from hospital.

Thoracoplasty

Two patients were culture positive at the time of transfer elsewhere two and six months after operation; the remainder were culture negative.

Conclusion and Summary

Thirty-six patients having major surgery for pulmonary tuberculosis were studied (twenty-five resection, eleven thoracoplasty). Organisms resistant to at least two of the standard chemotherapeutic agents were recovered from each patient before operation; antibacterial treatment over the operative period consisted of Viomycin with whatever other agent appeared most suitable. This was continued for an average period of twenty-three weeks.

Viomycin was discontinued in two patients because of side-effects; and the dosage was reduced in a further two who experienced no more trouble.

Apart from one post-operative bronchogenic spread of disease, no serious operative complication, and in particular no broncho-pleural fistula, was encountered.

It is concluded that Viomycin is a useful and reasonably safe agent for operative cover in the type of case described; it is felt that its use should be reserved wherever possible for this purpose.

Our thanks are due to Dr. D. E. Bottrill, who carried out the bacteriological investigations; and to Mr. H. A. Daniels, Mr. J. S. Glennie and Mr. P. Jewsbury, who operated on the patients.

REFERENCES

ADCOCK, J. D., DAVEY, W. N., HALEY, R. R., REES, R. M., and MEIER, W. A. (1954): *Amer. Rev. Tuberc.*, **69**, 543.

BARTZ, Q. R., EHRLICH, J., MOLD, J. D., PENNER, M. A., and SMITH, R. M. (1951): *Amer. Rev. Tuberc.*, **63**, 4.

BELL, J. W. (1956): *Amer. Rev. Tuberc.*, **74**, 169.

EHRLICH, J., SMITH, R. M., PENNER, M. A., ANDERSON, L. E., and BRATTON, A. C. (1951): *Amer. Rev. Tuberc.*, **63**, 7.

FINLAY, A. C., HOBBY, G. L., HOCHSTEIN, F., LEES, T. M., LENERT, T. F., MEANS, J. A., P'AN, S. Y., REGNA, P. P., ROUTIEN, J. B., SOBIN, B. A., TATE, K. B., and KANE, J. H. (1951): *Amer. Rev. Tuberc.*, **63**, 1.

FOSTER-CARTER, A. F., MYERS, M., GODDARD, D. L. H., YOUNG, F. H., and BENJAMIN, B. (1952): *Brompton Hosp. Rep.*, **21**, 9.

HOBBY, G. L., LENERT, T. F., DONIKIAN, M., and PIKULA, D. (1951): *Amer. Rev. Tuberc.*, **63**, 17.

HOUGHTON, L. E. (1954): *Lancet*, **1**, 595.

KARLSON, A. G., GAINER, J. H. (1951): *Amer. Rev. Tuberc.*, **63**, 36.

MURDOCH, J. McC., and STEWART, S. M. (1956): *Brit. J. Tuberc. Dis. Chest*, **50**, 85.

P'AN, S. Y., HALLEY, T. V., REILLY, J. C., and PEKICH, A. M. (1951): *Amer. Rev. Tuberc.*, **63**, 44.

PITTS, F. W., O'DELL, E. T., FITZPATRICK, M. J., DYE, W. E., HUGHES, F. J., and TEMPEL, C. W. (1953): *Dis. Chest*, **23**, 243.

SCHAFFELD, H. G., GARTHWAITE, B., and AMBERSON, J. B. (1954): *Amer. Rev. Tuberc.*, **69**, 520.

STEENKEN, W., and WOLINSKY, E. (1951): *Amer. Rev. Tuberc.*, **63**, 30.

WERNER, C. A., TOMPSETT, R., MUSCHENHEIM, C., and MCDERMOTT, W. (1951): *Amer. Rev. Tuberc.*, **63**, 49.

YOUMANS, G. P., and YOUMANS, A. S. (1951): *Amer. Rev. Tuberc.*, **63**, 25.

RESECTION IN PULMONARY TUBERCULOSIS

A REPORT ON 125 EXCISIONS IN 123 CASES

By S. E. Large, M.B.E., R. C. Curry and G. Kent Harrison
From The Connaught Hospital (Army Chest Centre), Hindhead

Introduction

The Connaught Hospital is the Army Chest Centre and thoracic surgery has been carried out here since October 1953.

This paper is a preliminary report on 125 consecutive resections in 123 patients for pulmonary tuberculosis performed between October 1, 1953, and December 31, 1955.

It is intended to show that in young patients with localised disease resection is a relatively safe procedure which need not involve them in long periods off duty.

Material

The Connaught Hospital receives cases of tuberculosis from the British army all over the world, and the patients comprise regular and national service soldiers as well as members of the women's forces and army families.

Because the cases are drawn from a healthy group which is closely supervised medically, advanced chronic pulmonary tuberculosis is not as commonly seen at the Connaught Hospital as it is in most civilian centres. Furthermore such cases, when they are admitted here, are usually advised to accept transfers to civilian institutions which can continue to supervise their treatment not only whilst they are in hospital but after they have been invalided from the army and are back at work in civil life. On the other hand, the Army Chest Centre receives a relatively larger proportion of two types of case than do most civilian centres. They are, first, cases of early active pulmonary tuberculosis in young adults and, secondly, cases of symptomless disease which have been discovered by routine X-ray or mass miniature radiography.

It is from these that the majority of cases in this series have been derived.

The Cases Operated On

Table I shows the types of disease for which resections have been done.

Table I

1. Solid lesions, usually symptomless, which changed little or not at all on pre-operative chemotherapy. All with negative sputa	7
2. Tuberculous disease remaining after a pre-operative course of bed rest and drugs which had caused some radiological clearing before resection	
(*a*) Non-cavitated at time of operation .. .. Sputum at operation. POS = 0 NEG = 98	98
(*b*) Cavitated at time of operation .. .. Sputum at operation. POS = 0 NEG = 13	13

(*Received for publication September* 28, 1956.)

TABLE 1—(*continued*)

3. Solid disease operated on before radiological stability had been reached because diagnosis was in doubt:
   - Suspected lung abscess 1
   - Suspected carcinoma 3
   - (All subsequently proved tuberculous: all had negative sputa.)
4. Advanced chronic pulmonary tuberculosis 1
   - Sputum at operation. POS = 0
   - NEG = 1
5. Destroyed lung and tuberculous empyema 2
   - Sputum at operation. POS = 1
   - NEG = 1

The average age of the patients operated on was 24 years. The youngest was 17 and the oldest 49 years of age.

110 of the patients were male and 13 female.

75 of the lesions operated on were on the right side and 50 on the left.

INDICATIONS FOR RESECTION

Cases for resection can be divided into two main groups: those in whom the disease remains active in spite of bed rest, anti-bacterial drugs and relaxation measures such as pneumoperitoneum, and those in whom the disease has already been stabilised by these means.

The majority of our cases belonged to the second group, and surgery was undertaken because it was considered that removal of the diseased area of lung offered the best safeguard against subsequent breakdown of the disease. We have regarded resection as the treatment of choice in all such cases except those with disease too extensive to permit its removal or those with so little radiological evidence of disease remaining after medical treatment that it was felt justifiable to leave them.

It has often been difficult in these minimal cases to decide which should be left alone and which resected, and it is probable that in this centre we have resected some lesions which other chest physicians and surgeons might have left alone. Our reasons for doing this will be given later.

THE EXTENT OF LUNG REMOVED

Table 2 shows the amount of lung removed at the operation.

TABLE 2

		%
Wedge resections	7	5·6
Segmental resections:		
1 Segt.	45	36·0
2 Segts.	34	27·2
3 Segts.	6	4·8
Lobectomy:		
1 lobe (by definition left upper lobe includes the lingula)	27	21·6
1 Segt.	3	2·4
Pneumonectomy	1	0·8
Pleuropneumonectomy	2	1·6

In 105 cases the amount of lung tissue excised appeared to equal the extent of the disease present as judged radiologically immediately before operation and by palpation at operation.

In 7 cases the tissue excised was in excess of the amount of tissue diseased by one segment or more.

In 13 cases tissue excised was less than disease present. These cases fall into two groups: (*a*) those in which the disease was ipsilateral (7 cases), and (*b*) those in which the disease was contralateral (6 cases).

In the first group (7 cases) all the cases had the main focus excised, only small shotty or millet-seed nodules being left behind which in no case numbered more than 5.

In the second group (6 cases) 4 cases had minimal disease on the other side which it was considered did not warrant operation. In 1 case operation was proposed for the contralateral side but was refused. In 1 case (that listed as advanced chronic pulmonary tuberculosis) where disease was advanced and bilateral, surgery was confined to removing a giant cavity that occupied the whole of the upper zone of the left lung.

Pre-operative Treatment

Every patient had a course of bed rest and anti-tuberculosis drugs before operation, together with postural retention and pneumoperitoneum in selected cases. The duration of this course varied according to the type of disease and response to treatment, but the average duration of preoperative treatment was five and a half months with extremes of one week and ten months.

The principle was followed that the optimum time for resection was when maximum improvement by non-surgical means had been achieved, and this was judged mainly on the radiological and tomographic appearances, although sputum, weight, E.S.R., T.P.R. and general condition all played a part in deciding when to operate.

The usual combination of drug was Streptomycin 1 G. and Isoniazid 200 mg. given daily for one month and then on alternate days, but towards the end of the series we began to give drugs daily for three months before reducing them to alternate days. A small number were given Streptomycin 1 G, and Para-amino Salicylic acid 20 G. daily for one month, after which the Streptomycin was reduced to 1 G. on alternate days, the PAS being continued daily.

One patient was given PAS and INAH throughout as she was intolerant of Streptomycin.

No instance of resistance to any of the drugs used occurred throughout the series.

Before operation each patient was taught diaphragmatic and lower costal breathing exercises which were continued after operation under the direction of the physiotherapist.

Operative Details

The chest was opened through the fourth intercostal space, and once the lung had been freed a bronchial clamp was applied to the main bronchus in all cases.

Excision of lung tissue was performed by standard technique.

Raw areas of lung following partial resection were oversewn with catgut.

In the first half of the series phrenic crush was carried out on all cases where more than a wedge resection had been performed. In the second half of the series phrenic crush was not performed in any case of resection except for both cases of pleuropneumonectomy.

In only three cases was a space reducing thoracoplasty performed.

Apical and basal tubes were inserted in all cases.

Post-operative Management

A negative pressure of about 90 cm. water was normally applied to the drainage tubes, which were routinely left in for forty-eight hours and then removed if no air leak was present and the lung had expanded.

Patients were nursed for three to four hours on the sound side with the operated side uppermost: thereafter they were nursed sitting up.

Four days after operation patients were encouraged to get up for toilet purposes and to sit in an armchair for an hour a day, but otherwise bed rest was continued for four weeks after operation.

During the first half of the series we aimed at beginning upgrading (at a rate of one hour every ten days) six weeks after operation. For the remainder of the cases we began upgrading four weeks after operation, this régime being delayed if significant complications were still present at that time. The 2 cases of pleuropneumonectomy and the 1 case of chronic advanced tuberculosis also had their dates for upgrading delayed.

When patients were up for seven to eight hours a day (that is, about thirteen weeks after operation) we discharged them on eight weeks' convalescent leave, provided (*a*) that there was no clinical or radiological evidence of reactivation or spread of disease, and (*b*) that apart from pleural thickening the lung on the affected side had completely filled the thoracic cage.

Regular army patients (of whom there were 30) were reviewed at the end of their convalescent leave and then returned to restricted duty in the lowest medical category.

Civilian patients—that is the female patients and those servicemen who had been invalided from the army, yet continued treatment in this hospital—were discharged to the care of their local chest clinic when up over seven hours. Under our own régime these cases would normally have returned to light work twenty-one weeks after operation.

Chemotherapy was continued as before operation until discharge from hospital.

Complications

These are listed in Table 3.

Table 3

		%
Deaths	3	2·4
Hæmorrhage	2	1·7
Broncho-pleural fistula	8	6·2
Empyema	3	2·4
Pulmonary embolism	1	0·8
Atelectasis	4	3·2
Hydrothorax / Pneumothorax	5	4·0
Spread or recurrence of disease	0	—

Notes on Complications

Eight patients developed broncho-pleural fistulæ; 4 were successfully treated by suction; 1 required open operation for its closure; 3 developed empyema which required drainage.

Four patients developed post-operative or lobar atelectasis which reaerated completely following physiotherapy. Post-operative bronchoscopy was not required on any occasion.

Our attitude to air and fluid in the chest post-operatively (hydro-pneumothorax) has been very conservative. Small collections of air or fluid were left alone. The question of when to intervene was tackled empirically. Generally speaking, collections of air or fluid were aspirated only if they appeared to be increasing or if they did not appear to be disappearing spontaneously after a few days' observation.

Thus only 5 patients with post-operative hydropneumothoraces required aspiration, and 2 hæmothoraces. The remaining cases were treated conservatively, and in all but 2 the air and fluid had absorbed completely by the time they were discharged. In these two, small air spaces remained which were rapidly diminishing in size at the time of discharge from hospital.

Taking the post-operative complications as a whole, we found that in only 4 patients (3 with empyema and 1 with broncho-pleural fistula) was it necessary to delay the date of their upgrading or the date of their discharge from hospital. In these cases, discharge was delayed by three months, five weeks, four weeks and two weeks.

Deaths

One death occurred in a man aged 44 who suffered a myocardial infarction ten days after operation.

One death occurred in a patient who had had a pleuropneumonectomy, and who required a thoracotomy three weeks later on account of continual pyrexia for which no cause could be found. His heart stopped while being positioned on the table for the second operation and he died four hours later.

One death (early in the series) occurred in a man aged 20 who developed a massive hæmorrhage four hours post-operatively.

Spread or Recurrence of Disease

No case of spread or recurrence of disease occurred in the immediate post-operative period (thirteen weeks). No follow-up has yet been attempted on those patients who had been discharged from the army. Those patients that remain in the army are reviewed at regular intervals. There have been 30 of these patients, all regular soldiers, of whom 1 has been back at restricted duty two and a half years; 15 for more than one year and the remainder between six months and one year. Up to October 1956 there has been no recurrence or spread of disease in any of these cases.

The indications for resection in tuberculosis have been stated many times. They include persistent cavities; solid disease of more than 1 or 2 cm. in extent;

destroyed lungs; tuberculous bronchostenosis or bronchiectasis; tuberculous empyemata; broncho-pleural fistulæ and failed thoracoplasties.

In our series, 4 cases were resected because the diagnosis was in doubt; 7 were cases of isolated symptomless foci; 1 case had advanced chronic pulmonary tuberculosis and 2 cases had empyema with extensive underlying lung disease.

The great majority of cases, however, were young people with active tuberculous infiltration which had reached a state of stability on medical treatment and in whom further improvement was judged unlikely. There were 111 cases of this type (98 non-cavitated and 13 cavitated) all with negative sputum and most with localised disease. Thus the series was limited both as regards the type of case and the age groups concerned.

Operation was clearly indicated in the case of advanced chronic disease and in the 2 cases of empyema; in these patients the only alternative to operation was chronic invalidism.

Likewise, resection was logical in the 4 cases subjected to thoracotomy because of diagnostic doubt and in the 13 cases in which cavities could not be closed by medical means alone.

There remain for discussion the 7 cases of isolated symptomless solid foci and the 98 cases of solid disease—often strictly localised—which had reached stability after a course of medical treatment.

It is in this type of case that the place of excision as a definite form of treatment is most debatable, for, unlike more complicated and extensive forms of tuberculosis in which there is often no alternative to surgery except chronic invalidism, here there is a well-tried alternative in the form of upgrading under the cover of anti-tuberculous drugs.

When deciding which form of treatment to employ, many factors have to be taken into consideration, the more important of which are the likelihood of the disease (if it is unresected) breaking down in after life; the operative risk of resection; the chances of reactivation of disease after operation; and the length of time before a patient can be cured and returned to work. Less important, but also relevant, are economic and social factors.

It is impossible to state accurately what proportion of cases would have broken down later if left unresected. Clinical experience over the past suggests a not inconsiderable number. Hobby *et al.* (1954) and Todd *et al.* (1956) have shown that even after several months of chemotherapy tubercle bacilli can still be cultured from a large proportion of solid lesions removed at operation. Furthermore it is impossible to say on clinical and radiological grounds alone which are sterile and which are not, and their removal by operation would seem a logical procedure provided it can be done safely and without involving the patient in a long period of disability.

With regard to the operation itself, we have had three deaths one of which occurred after a pleuropneumonectomy, one was due to a coronary thrombosis apparently unconnected with the operation, and one was due to a massive hæmorrhage and occurred early in the series.

The complications have been few, and in only 4 cases have they resulted in any delay in the date of discharge from hospital. In the other cases in which complications occurred, they had cleared up completely by the time the patient

came to be discharged and it was not considered necessary to delay their discharge from hospital and subsequent return to work.

We consider the low complication rate was due partly to the fact that the majority of patients operated on were young and partly to the conservative attitude we have taken to those complications which did occur.

Our usual post-operative régime in the uncomplicated cases is a short one, consisting of four weeks' bed rest (six weeks in the early cases) followed by nine weeks' upgrading and a return to light work or to restricted duty within twenty-one weeks of operation. We feel a longer period than this is unjustifiable in young persons who have had adequate pre-operative and post-operative chemotherapy and in whom all radiologically visible and palpable disease has been excised at operation.

The majority of our cases have in fact been able to leave hospital as intended thirteen weeks after operation. The exceptions have been those who died: the case of chronic advanced tuberculosis in which some significant disease remained after operation and the 4 cases whose complications necessitated some delay in the date of their discharge.

Of those patients discharged thirteen weeks after operation, the army patients were returned to restricted duty eight weeks later, that is twenty-one weeks after operation. Under our régime the civilian patients (who had by then come under the care of civilian chest clinics) would also have been returned to work at twenty-one weeks.

If these patients had not been treated by resection, but had been given a course of sanatorium upgrading instead, it is unlikely that they could have been returned to work appreciably earlier.

Furthermore, we feel that young patients who have had resections of all visible and palpable disease will be able to return to full work, and even to heavy work, sooner than those not so treated; for the latter patients will be left with areas of solid disease in their lungs which will require observation over many years before they can be considered healed and unlikely to break down under stress.

This is a matter of particular significance in army patients, for it means that after resection a soldier can eventually be returned to a " normal " medical category, whereas after medical treatment alone this is justifiable in very exceptional cases only. Thus not only is the individual's career not jeopardised (for in a low category his promotion to the higher ranks is affected), but the army can retain the services of many officers and N.C.O.s who would otherwise have to be invalided out of the service or at best be employed in restricted appointments.

Lastly, there are social and economic factors to be considered. Many of the cases we deal with at the Connaught Hospital are young men either on army pay or pension. If their lesions are left unresected, and break down later, they may involve the patients in long-term treatment at a time in their lives when, because of financial, career or family reasons, they can afford time off less easily than the present. Resection spares them the anxiety and uncertainty of harbouring potentially dangerous foci in their lungs and it may enable them to obtain employment which would otherwise have been closed to them.

Summary

A report on 125 consecutive resections in 123 patients at the Army Chest Centre has been presented.

The majority of these patients were young and had relatively localised disease. In these, operative mortality was low and the complication rate negligible.

Patients were normally discharged from hospital thirteen weeks after resection and returned to restricted duty or light work twenty-one weeks after operation. These times compare favourably with what might have been considered reasonable had medical measures alone been employed.

REFERENCES

Hobby et al. (1954): *Amer. Rev. Tuberc.*, **70**, 191.
Todd, G. S., Teare, D., and Gordon, W. I.(1956): *Lancet*, **ii**, 1.

ARTIFICIAL PNEUMOTHORAX UNDER CHEMOTHERAPY

By Brian C. Thompson
Windsor Chest Clinic

How far is it true to say that in the treatment of pulmonary tuberculosis (Lloyd, 1955) "there is no place for artificial pneumothorax to-day"? The excellent results obtained, with uniform control, before the introduction of chemotherapy (Ellman and others, 1956; Roberts and Lyons, 1955) seem to have been forgotten, more in this country than on the Continent (Pines, 1955), and though Foster-Carter (1954) considers that "the procedure should not lightly be discarded," this in fact is what has happened. Livingstone (1955) has called for a new assessment of the method, used in conjunction with those anti-microbial drugs which are now by themselves a standard treatment. This paper is an attempt to answer that challenge.

Material

One hundred consecutive A.P. inductions in patients of the Windsor Chest Clinic, performed in conjunction with streptomycin, PAS and Isoniazid in varying combinations of two or three, have been taken for study. Only those cases were excluded where the A.P. was abandoned as useless in the first weeks or after ineffective thoracoscopy. The inductions were performed between the middle of 1949, when combined chemotherapy came into use here, and February 1954, thus giving a minimum observation period of two years (Table I). A level rate of A.P. inductions was maintained over the period of study.

Table I.—Year of Induction of 100 Cases of A.P.

Year:	*1949*	*1950*	*1951*	*1952*	*1953*	*1954*
Number of Cases:	6	23	24	20	22	5

Ninety-four patients were involved, the A.P. being bilateral in 6 cases. Forty-seven of the 94 patients were males and 51 of the 100 A.P.s were in male patients. Forty-three of the unilateral A.P.s were on the right and 51 on the left side. The age and sex distribution is shown in Table II.

Table II.—Distribution by Age and Sex

Years of Age	*10-14*	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40+*	*Total*
Male ..	1	3	10	13	7	7	10	51
Female ..	1	7	17	10	6	3	5	49
Total ..	2	10	27	23	13	10	15	100

(*Received for publication September* 26, 1956.)

Indications for choosing A.P. treatment were orthodox: disease of small to moderate extent reduced by preliminary treatment from a more extensive and more active state; this preliminary treatment included bed rest and chemotherapy, of combined type, for at least several weeks; cavitation proved or presumptive, almost always with tubercle bacilli in the sputum at some stage, a cavity tending to persist, but not obviously under tension and not greater than 3 cm. in diameter; disease mostly confined to an upper lobe; toxæmia controlled and sedimentation rate around normal; in general, absence of accepted contra-indications (Houghton, 1954), including any substantial degree of irreversible lung damage. Thoracoscopy was performed in all cases and A.P. continued only where a reasonably free pleura was achieved. Routine bronchoscopy was not performed, but gross endobronchitis was judged to be absent, though not always correctly, as events showed.

The presence of contralateral disease, its nature and any selective treatment of it, have been ignored so far as possible in the assessment of results. The 6 patients with bilateral A.P. have been treated in most respects as 12 separate cases. Three patients had had A.P. treatment completed on the other side. Three patients, whose A.P.s come into this study, underwent contralateral thoracoplasty as part of planned treatment. Two others had, in addition to their A.P., an artificial pneumoperitoneum for a short period.

Results

The pneumothorax has been terminated and the lung expanded in all cases. Cessation of collapse treatment was by choice in 64 cases. In the other 36 cases it was premature, for reasons given in Table III.

Table III.—Causes of Premature Cessation of A.P.

	Male	*Female*	*Total*
1. Loss of A.P. space	2	8	10
2. Repeated spontaneous pneumothorax ..	3	—	3
3. Persistent cavitation/positive sputum ..	8	2	10
4. Pleural effusion/atelectasis	8	3	11
5. Spread of disease	1	1	2
Total	22	14	36

Premature Cessation of A.P.

1. *Loss of Space*

Of the 10 patients in whom this occurred, 7 of whom were young women, 2 had had previously some fluid in the A.P., so that subsequent obliterative pleuritis was not unexpected. Otherwise obliteration came quite suddenly and soon became complete. As may be seen in Table VII, it was usually deferred long enough for cavity closure to be maintained a year or more, and in only 1 patient has reactivation so far occurred.

2. *Repeated Spontaneous Pneumothorax*

Two middle-aged male patients, 1 with bilateral A.P., gave evidence at a rather late stage of sub-pleural emphysematous bullæ, which tended to rupture so inconveniently that refills had to be stopped. The second of these patients has had a late relapse and is again under treatment.

3. *Persistence of Cavity*

Persistent bacilli in sputum (4 cases) or radiological cavitation (6 cases) but without segmental collapse, in a lung with a technically good A.P., led to the discontinuation of the latter in 10 cases. Three of these patients had resectional surgery, 1 of them dying on the operating table; 1 had artificial pneumoperitoneum and 1 a phrenic nerve crush. In the other 5 cases, cavity closure was achieved by lung re-expansion and chemotherapy alone, but in 2 of these the cavity reopened later.

4. *Pleural Effusion and Atelectasis*

There were 8 cases of the former and 3 of the latter, sufficiently persistent for the A.P. to be abandoned. In no case did the effusion reach a purulent stage. Seven cases were successfully treated by chemotherapy alone, 2 had no treatment, 1 had artificial pneumoperitoneum and 1 thoracoplasty.

5. *Spread of Disease*

Spread of disease on the A.P. side in 1 case and contralateral spread in another led to abandoning the A.P. in favour of thoracoplasty in the former and pneumoperitoneum in the latter.

Review of these 36 cases in the light of knowledge subsequently gained suggests that longer and more intensive preliminary chemotherapy would have substantially reduced the incidence of pleural effusion, atelectasis and persistent cavitation, by clearing up the endobronchial tuberculosis usually responsible for these complications.

Better refill technique might have preserved the air space in some cases.

TABLE IV.—AGE IN RELATION TO FATE OF A.P.

	10-14	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40+*	*Total*
Number of inductions	2	10	27	23	13	10	15	100
Number ceased prematurely ..	—	4	5	10	3	4	10	36
Percentage ceased prematurely	—	40·0	18·5	43·5	23·2	40·0	66·7	36·0

Faulty judgment in case selection was sometimes to blame. The high incidence of premature loss in the older age groups (Table IV) is, to some extent, attributable to unhealed tuberculous endobronchitis, as shown in Table V, but other factors associated with middle age, such as the emphysema which ought to have contra-indicated 2 other cases, were probably not given enough weight.

TABLE V.—AGE IN RELATION TO COMPLICATIONS OF A.P.

	10-14	15-19	20-24	25-29	30-34	35-39	40+	Total
1. Loss of space	—	2	2	5	—	—	1	10
2. Spontaneous pneumothorax	—	—	—	—	—	1	2	3
3. Persistent cavitation ..	—	1	1	2	1	1	4	10
4. Effusion/atelectasis ..	—	1	2	2	1	2	3	11
5. Spread of disease	—	—	—	1	1	—	—	2
Total complications ..	—	4	5	10	3	4	10	36
Total inductions ..	2	10	27	23	13	10	15	100

A.P. DISCONTINUED FROM CHOICE

A.P. treatment was brought to a close voluntarily in 64 cases, after periods ranging from eighteen months to four and a half years; sometimes early because of technical difficulties or because pleural thickening was observed or suspected; sometimes late, because the patient requested its prolongation, having learned to rely on its support. Chemotherapeutic cover was not as a rule employed, and there were no notable complications such as pleural effusion.

The immediate clinical result was excellent in all cases but two where a cavity reopened immediately. Though A.P. had been maintained for over three years in each case, we must suspect that true cavity closure and bronchial healing had never been achieved, and that collapse of the lung had merely masked latent activity. So far there have been no other instances of local recurrence and no evidence that early discontinuation of A.P. carries additional risk.

PRESENT CLINICAL CONDITION OF 94 PATIENTS

Of 59 patients in whom 64 A.P.s were discontinued by choice, 56 became apparently cured and have remained so without any further treatment. In 2 others, a cavity reopened in the re-expanded lung, but was cured by resectional surgery. One patient is under treatment for fresh disease in the opposite lung.

Of 35 patients with 36 A.P.s lost or involuntarily given up, 24 became apparently cured without further treatment except chemotherapy in some cases. Five are cured after other collapse therapy and 2 after resection. One died under surgery. Three are under treatment for re-activated disease.

Four patients with bilateral A.P. feature in both the above groups. Of the total 94 patients, 80 may be regarded as cured directly by A.P. plus chemotherapy, 5 after other collapse measures on the same side, 3 pneumoperitoneum, 1 phrenic crush and 1 thoracoplasty, and 4 after surgical resection of 1 lobe or less; 4 have active disease, 1 is dead. Three patients had thoracoplasty on the opposite side, as planned before induction of A.P.

All lungs are fully re-expanded except one, where a small effusion persists, but no air, and another case was discontinued too recently for consideration. There was no case of " unexpandable lung."

Functional Results

The end result of 92 A.P.s, that is 61 terminated from choice and 31 given up involuntarily, excluding 8 cases where subsequent surgical or other measures make it impossible, may be considered in relation to respiratory function. We are obliged in this context to count individual lungs, not patients.

In the absence of laboratory tests, no great accuracy is possible. Judgment has been based on X-ray appearances, supported to some extent by physical examination and, in cases where the other lung is good, by the patient's subjective exercise tolerance.

The following standards have been adopted:

Grade I. Pleural thickening not apparent or not more than blunting of the costo-phrenic angle.

Grade III. Gross pleural thickening. Mediastinal displacement. Hemidiaphragm elevated and/or limited in excursion. Subjective shortness of breath.

Grade II. Intermediate between the other two grades, with not more than one feature of those listed under Grade III.

Table VI.—Functional Result in 100 Cases of A.P.

	Functional Grade				
	I	*II*	*III*	*Unclassified**	*Total*
Cases terminated from choice ..	33	20	8	3	64
Cases terminated prematurely ..	12	14	5	5	36
Total ..	45	34	13	8	100

* *E.g.*, because of subsequent surgery.

The totals in each grade (Table VI) show that almost half the A.P.s, however terminated, left little or no visible deformity. Only 13 were grossly affected radiologically. In the remaining 34 cases the residual pleural thickening was no more than may commonly be seen after a lobar resection or an uncomplicated primary pleurisy with effusion.

There was no substantial difference in results between A.P.s terminated from choice and those abandoned involuntarily; nor, considering the latter group of 31 cases, between those lost from spontaneous obliteration and those given up after pleural effusion or atelectasis.

The influence of the duration of A.P. in producing more or less pleural thickening is shown in Table VII. It appears that this has little effect, whether termination was from choice or otherwise, except that in A.P.s voluntarily terminated in less than two years a high proportion was left with a pleura normal or nearly so.

The sex of the patient did not seem to affect the functional result.

It has been found unfruitful to consider the type and duration of the individual lesion in relation to functional results, because of difficulties in

classification. In general, it seems that young patients of either sex, with presumably fairly recent disease, giving a good initial response to chemotherapy, and with A.P. maintained only a year or so, gave the least trouble and were left with the clearest and most useful lungs.

TABLE VII.—FUNCTION RELATED TO DURATION OF A.P.

Duration of A.P. grade	*A.P. terminated from choice*				*A.P. terminated prematurely*			
	Functional grade				*Functional grade*			
	I	*II*	*III*	*Total*	*I*	*II*	*III*	*Total*
6m.-1 year	—	—	—	—	7	5	—	12
1-2 years	7	2	1	10	7	6	1	14
2-3 years	11	4	3	18	1	3	1	5
3 years + ...	15	14	4	33	—	—	—	—
Unclassified				3				5
Total ..	33	20	8	64	15	14	2	36

Discussion

These results indicate that A.P. in conjunction with chemotherapy is a safe curative treatment for cavitary pulmonary tuberculosis. Empyema and unexpandable lung, formerly dreaded complications, did not occur in this series. Even where the treatment was failing to achieve its object, or where refills were stopped for some other reason, the ultimate result was usually good. Only 7 out of 34 patients required further active measures for immediate arrest of the disease, including 3 cases of major surgery.

Relapse occurred after voluntary termination of A.P. in 2 cases and in 4 others some time after loss of the air space. The only other relapse to date has been a case of contralateral spread.

Gross residual thickening of the pleura is present in 13 cases, 5 of which were preceded by no complication and were possibly unpredictable. Only in this small group could one say that the patient was ultimately worse off because of his A.P., or rather that the price paid for cure by this method was perhaps too high. However, it must in fairness be measured against alternative methods.

In the period concerned—a necessary reservation, for opinions change rapidly—there is little doubt that the alternative to A.P. in most cases in this series, and one which many physicians would have preferred, would have been resection, often of a whole lobe. Even today, Muschenheim (1955) considers that the indications for A.P. and resection are almost identical. As in this series the disease was usually in an upper lobe, resection would doubtless often have included thoracolysis: a traumatic experience for the patient, expensive in hospital care and productive of substantial pleural thickening and loss of function, as has been measurably demonstrated by Taylor and others (1955).

Artificial pneumothorax is therefore not inferior under this head. Whether resection gives better and more lasting results is another matter, but this has not yet been proved. It is not irrelevant at this point to remark that the only death in this series was during a resection operation.

Artificial pneumothorax is a reversible procedure, resection is permanent. Unsuccessful A.P. can be succeeded by resection. The converse does not apply. Lesions resected after chemotherapy often show only " burnt out " tuberculosis, with the disease apparently well healed. The bronchi are healthy and cavities previously seen by X-ray are either smooth-walled and epithelialised or replaced by secondary cyst formation. Acid-fast bacilli, if recovered at all, may be found unviable or at least avirulent (Ware, 1956). The pathologist may be unable to say whether the specimen should have been removed or could safely have been left in the patient's body. It certainly cannot be put back again.

Just as A.P. was never shown, in pre-chemotherapeutic days, to be statistically superior to conservative sanatorium treatment (though most people regarded such superiority as self-evident), so to compare it with resectional surgery is itself likely to be futile, at any rate pending long-term studies of surgical results. A challenge to both methods comes most opportunely from advocates of a very prolonged chemotherapeutic régime, unsupported by ancillary treatment, the results of which are now becoming available. Recently Hoyle (1956) and his associates have shown that cavitary phthisis can be cured by drugs alone, if given intensively over long periods, even in cases of extensive disease, formerly thought fated for more radical measures. Similar work by Ross and Kay (1956) confirms the view that resectional surgery, at any rate, should be held even longer in reserve. Unfortunately, the only criterion for cavity healing by chemotherapy alone may be the continued absence of acid-fast bacilli from the patient's sputum, since annular shadows often persist, so that long-term assessment is difficult (Weir and others, 1956). May it not be that conversion of the cavity into a linear or stellate scar, which commonly results from a successful A.P., inspires more confidence, both in patient and physician.

In the present series, a common indication for A.P. induction was the apparent failure of initial chemotherapy to produce cavity closure. Had the drugs been used better or more persistently, perhaps in some cases nothing further might have been required. On the other hand, it is likely that even better A.P. results would have been obtained had the concomitant drugs been employed in the light of knowledge subsequently acquired; isoniazid, for instance, was not known when our series began. Impressive results have been claimed by Birath (1955) from the use of a special A.P. technique in conjunction with combined intensive chemotherapy, achieving not only a high rate of cure but also a negligible loss of ventilatory function in 95 per cent. of cases.

There is thus little doubt that chemotherapy is a valuable adjunct to A.P. That A.P. may be a valuable adjunct to chemotherapy is another matter. Among opponents of the method, Woodruff and others (1955) have gone so far as to condemn it as a positive hindrance, on the theory that an atelectatic and relatively avascular portion of lung will have a reduced exposure to blood-borne anti-microbial drugs. This view is strongly contested by Cutler (1955) and cannot be supported by observations from the present series.

If it is agreed that A.P. gives good results with chemotherapy, both curative and functional, and is becoming increasingly harmless, the giving of refills would still be a burden to clinics and the receipt of them a nuisance to the patient. There may sometimes, however, be a positive gain in the regular

obligation to attend the clinic, especially in the case of a rash or irresponsible patient, for whom close observation is desirable and to whom some discipline and the good example of other patients, regularly encountered, may be a steadying influence. The belief is becoming widespread, *mirabile dictu*, that pulmonary tuberculosis is not nowadays a serious matter—" no worse than a cold in the head," as a medical colleague said recently. While we must welcome the disappearance of the chronically anxious ex-sanatorium patient, over-optimism carries another kind of hazard. An unreliable patient cannot be trusted to take regularly and in sufficient dosage for months or years the drugs prescribed for him. Attendance for refills greatly facilitates his control.

Summary and Conclusions

One hundred consecutive cases are described where artificial pneumothorax was induced after anti-microbial chemotherapy.

The treatment has been brought to a conclusion in all cases, and the results are considered from both a curative and a functional aspect.

Complications were fewer and less serious than in pre-chemotherapeutic times and it is likely that even better results would have been achieved with the full range of drugs now available, and their better employment.

As it is evident that artificial pneumothorax can now be used with freedom from most, if not all, of its major drawbacks, its place in the treatment of pulmonary tuberculosis is due for fresh consideration.

It is suggested that there are certain cases where artificial pneumothorax may be preferable to surgical resection, and other cases where a long-term chemotherapeutic régime may benefit from its support.

REFERENCES

Birath, G. (1955): *Svenska Lakt.*, **52,** 184.
Cutler, J. W. (1955): *Amer. Rev. Tuberc.*, **71,** 600.
Ellman, P., Johnson, J. H. P., and Kagan, K. (1956): *Brit. J. Tuberc. Dis. Chest*, **50,** 130.
Foster-Carter, A. F. (1954): *Brit. med. Bull.*, **10,** 150.
Houghton, L. E. (1950): *Tubercle Lond.*, **31,** 50.
Hoyle, C., Nicholson, H., and Dawson, J. (1955): *Lancet*, **2,** 1310.
Livingstone, J. L. (1955): *Brit. med. J.*, **1,** 243.
Lloyd, J. W. (1955): *Brit. med. J.*, **1,** 538.
Muschenheim, C. (1955): *Amer. Rev. Tuberc.*, **72,** 1.
Pines, A. (1955): *Tubercle Lond.*, **36,** 319.
Roberts, B., and Lyons, J. P. (1955): *Tubercle Lond.*, **36,** 187.
Ross, J. D., and Kay, D. T. (1956): *Thorax*, **11,** 1.
Taylor, W. J., Petter, J. B., and Whittenberger, J. L. (1955): *Amer. Rev. Tuberc.*, **72,** 453.
Ware, P. F., Stauss, H. K., Dillon, R. J., and Tempel, C. W. (1956): *Amer. Rev. Tuberc.*, **73,** 165.
Wier, J. A., Storey, P. B., Tempel, C. W., and Weiser, O. L. (1956): *Amer. Rev. Tuberc.*, **73,** 117.
Woodruff, C. E., Steininger, W. J., Jones, E. M., Klopfenstein, M. D., Mueller, E. Z., and Howard, W. L. (1954): *Amer. Rev. Tuberc.*, **70,** 533.

PULMONARY TUBERCULOSIS IN OLD AGE

By O. D. Beresford

From the Bournemouth Clinical Area

Pulmonary tuberculosis in old age is a well-recognised entity.

Old age is a vague term. Myers (1952) and Barber (1953) accepted 50 and upwards as aged. Snell (1941) spoke of senile tuberculosis in those over the age of 60. Auerbach (1940) avoided the term and preferred to write of the older age groups, accepting those who had reached 40 in his survey of the pathology of tuberculosis. For the purpose of this work, those who had reached the age of 65 years were considered old. The increased span of life in modern times must lead to a readjustment of views on the diseases that occur when life is drawing to its close, and pulmonary tuberculosis occurs sufficiently often to be of considerable importance. Old people are apt to be careless in their habits and an undiagnosed case of pulmonary tuberculosis can have serious results. The necessity for finding the infectious case of tuberculosis becomes more urgent as we see the possibility of this disease at last coming under control, and if a substantial number of cases occur in old age, they must be sought and brought under surveillance.

For this reason, an analysis was made of all patients over the age of 65 years diagnosed as having pulmonary tuberculosis during the period from 1950 to the end of 1955. The clinic register of tuberculous patients in this area is approximately 950, and of these 150 were found to be aged. There were 98 males and 52 females. The preponderance of elderly males with pulmonary tuberculosis has been commented on by previous authors, but no satisfactory explanation has been given for the sex incidence, although Heaf (1955) considered it might be due to changes in the endocrine system and in particular to the secretion of corticotrophin.

The circumstances of this town are exceptional in that many old people come here to retire, but old people occur in all areas and the analysis of this group of patients should prove of interest not only to chest physicians but to general practitioners, geriatricians and public health authorities.

Of these 150 patients, 115 are still alive, 75 males and 40 females. Of these, 37 males and 8 females are persistently sputum positive. Because of carelessness, forgetfulness or some other reason, there is considerable difficulty in obtaining adequate sputum examination in old people, and in 25 cases the investigation had not been done sufficiently often. In the absence of sputum, laryngeal swabs were not taken unless some special indication was present.

There were 64 known aged patients on the register prior to 1950, but in 51 patients the diagnosis had been made since then, and 12 of them were diagnosed in 1955. Eight were found following mass radiography, 4 as contacts, and 3 were referred following a diagnosis of tuberculous laryngitis. The remainder were referred by their private practitioners because of symptoms.

(*Received for publication October* 11, 1956.)

In 35 cases, the disease had been present for periods varying between 15 and 60 years. In 8 cases the disease had been known to be present for more than twenty years, and although little radiological change had occurred, sputum had been persistently positive.

It has often been stated that this disease is silent in old age. It is true that in some long-standing sputum-positive cases there were relatively few symptoms and surprisingly little disability. In the newly diagnosed cases or those who had shown recent spread of their lesions, the symptoms usually associated with tuberculosis were present, notably cough and sputum. There is a danger that in old people a cough is all too readily put down to bronchitis or smoking, and chest X-ray and sputum examination are not carried out.

The question of relapse in old age is associated with the need for continued surveillance when the disease is regarded as recovered or inactive. It has been our practice to continue at least yearly surveillance in such cases and this has resulted in several unexpected positive sputum results without radiological change. In the absence of serial X-rays and repeatedly negative sputum cultures, a diagnosis of " healed " disease must be accepted with some reserve.

Five patients showed spread of the lesions radiologically after having been apparently stable for many years. The appearances were consistent with bronchogenic spread and positive sputa were obtained. This may seem a small number, but because of the difficulty of re-discovering such patients, it seems that nowadays there is a strong case to be made for the continued surveillance of any patient who has had tuberculosis in the past, irrespective of age.

The decision to embark on active treatment in the elderly is not always easy. Some are very ill when first diagnosed and to make the remainder of their lives miserable with injections and numerous tablets seems wrong. Some refuse to accept treatment and others feel relatively well. The long standing sputum-positive case who has shown little change radiologically over the years and who feels well presents a most difficult problem. Benefit from active treatment symptomatically is doubtful, but from a public health point of view treatment would be desirable. The forgetful or unco-operative patient is probably better left untreated unless proper supervision can be ensured.

Nineteen cases received hospital treatment during the period under review although admission to hospital in old age presents particular problems. Pulmonary embolus is perhaps the most important and certainly the most lethal of the complications that may arise from putting an old person to bed. Prolonged bed for these patients was avoided as far as possible, and, if a patient felt well enough to get up for toilet purposes, this was encouraged.

Many of these patients live alone or are a burden to their families, and once in hospital are liable to become permanent residents; Geddes and Lowe (1952) commented on this problem.

It would seem most desirable to have a home solely for the care of the elderly tuberculous subject and would be far less expensive than a hospital bed. The London County Council established a hostel at St. Albans for the chronic infectious case which was eventually abandoned, but two further hostels have now been opened and are functioning successfully (Hartston, 1956). Nowadays, when small efficient sanatoria are being closed, second thoughts should prevail, as by suitable staff adjustments these could be run economically and would form

admirable units for the isolation, care and happiness of these elderly tuberculous subjects.

Thirteen patients were admitted to hospital for a short time only and then discharged home to continue their chemotherapy. Satisfactory results were obtained in some cases but in general the domiciliary treatment of the elderly tuberculous patient proved very difficult.

It was not surprising to find that in a little more than half the cases some associated disease was present. Unless specifically asked for, these conditions may not be mentioned, as all too often the patient attending a chest clinic considers it out of order to mention other troubles, even when they are obviously related. The conditions mentioned as complicating factors were bronchitis and emphysema (19), hypertension (10), cardiac lesions (7) and peptic ulceration (7). Three patients had emergency operations for perforation of an ulcer. Diabetes mellitus was present in 3 patients and the diagnosis of pulmonary tuberculosis was established after the diabetes in all 3. Arthritis was present in 3 and psychosis in 3. Bronchiectasis occurred in 2 patients and pernicious anæmia, pneumoconiosis, cerebral thrombosis, prostatic hypertrophy (necessitating operation), and cancer of the breast were noted on 1 case each. Extra-pulmonary tuberculosis occurred in 5 patients excluding those with tuberculous laryngitis. One had an abscess of the chest wall and 1 male patient had a cold abscess which appeared to originate from the breast. One had a tuberculous hip joint which had been present for many years, 1 had a tuberculous knee joint, and 1 a fistula-in-ano.

Death occurred in 35 cases, 23 males and 12 females. In 23 cases (15 male and 8 female) death could be attributed to the tuberculosis, as in all these cases the sputum was positive and in all except one the diagnosis had been established in recent years. In the remaining cases, some of whom were sputum positive, death was variously recorded as coronary thrombosis (6), cardiac failure (3), nephritis (2) and carcinoma of the breast (1). Tuberculous laryngitis was noted as a complication in 4 patients.

In all but 2 patients, the diagnosis had been made in recent years, but the history and radiological appearances disclosed that the disease had been long-standing in at least 12.

Little comment can be made on the management of these cases, as most occurred before long-term chemotherapy became an accepted method of treatment.

Contact examination is perhaps the most important part of the investigation and is particularly important when the patient continues to work in an occupation which brings him into contact with the general public. One sputum-positive case was actively engaged as a barman at the time of diagnosis and another as a café proprietor. In both these cases the spouse only was examined as a contact, but the potential field for infection was enormous.

In spite of a thorough and efficient system for the examination of contacts, none were examined in 75 cases. Many factors accounted for this, but the main difficulty appeared to be that old people live largely on their own and close contacts are difficult to find. The spouse, if there is one, is reluctant to attend a clinic, adopting the attitude of " What does it matter at my age? " The grown-up children who leave the home may be difficult to trace. Further-

more, over-zealous attempts to persuade contacts to attend may result in the loss of their lodgings and simply antagonise them, a most important practical consideration.

Of the remaining 75 cases, 188 contacts were examined. In 34 cases only one or two were examined, so the majority of contacts came from a relatively small number of index cases. The findings of Robins (1953) in this matter are of some interest. In his study of the age relationship of cases of pulmonary tuberculosis and their associates, he found half of the older males were without household associates, and in an additional 21 per cent. there was only one, presumably the spouse. Of 188 contacts examined in the present series, 6 were found to have lesions requiring treatment and 4 more developed lesions requiring treatment whilst under routine surveillance. In 2 cases a tuberculous kidney developed two years after the death of the parent, and in another case a pulmonary lesion appeared a year after the death of the source case. Seven were found to have calcified lesions. Previously known cases of tuberculosis amongst the contacts are not included in this analysis, but there were at least 14.

Almost a 5 per cent. yield from contact examination is impressive, but for the purpose of this work all contacts examined were regarded as coming from the elderly patient, even if the main contact was with the daughter or grandchild. Thus the elderly index case may be found following contact examination of a child with a positive tuberculin test or a newly diagnosed case. In one adolescent who developed a pleural effusion both the mother and the grandfather were found to have tuberculosis when examined, and in such an instance the daughter and grand-daughter would be included as contacts.

The results of the contact examination in this series of cases is shown in Table I.

TABLE I

Number of cases where contacts were examined	73
Number of cases where only one or two attended	34
Total number of contacts seen	188
Number who had lesions requiring treatment	6
Number who developed lesions requiring treatment whilst under surveillance	4
Number with calcified lesions	7
Number with minimal lesions	3
Number vaccinated with B.C.G.	35

Discussion

The paucity of the literature on tuberculosis in old age is a reflection of the apathy shown by the profession in the past to this important source of infection. This has been mentioned by some authors, and Medlar (1948) described old age as " the disregarded seedbed of the tubercle bacillus." Myers (1952) wrote on " tuberculosis lurking amongst the aged," and Barber (1953) wrote of it as " a geriatric problem." It is, however, more than a geriatric problem now that counter-measures can be taken. In an ageing population where tuberculosis is diligently sought and effectively treated in younger age groups, it is reasonable to suppose it will retreat into old age. Robins (1953) points out the figures appertaining to this in New York City and shows that the newly diagnosed cases

in older age groups have more than doubled in a generation. It is becoming more and more desirable to encourage these old folk to attend mass radiography surveys and be referred to chest clinics, and general practitioners can play a bigger part by referring old people with a chronic cough or vague ill-health.

Wilkins (1956) quotes figures obtained from the Ministry of Health for the notifications of men over the age of 65, which show that in the sixteen years from 1938 to 1954 their notifications had almost doubled.

Once the diagnosis has been established, active treatment can be undertaken in selected cases, and although there are problems to be faced, they are not beyond solution. Long-term chemotherapy, if necessary on an ambulant basis, and avoiding strict bed rest, can be expected to give satisfactory results. Perhaps more important is the significant and consistent sputum reduction and hence lessened opportunity for passing on the disease. Much care is required in the administration of the anti-tuberculous drugs. The well-known gastro-intestinal upsets caused by PAS are apt to be strongly resented by the aged and a voluntary reduction in drug dosage may occur without the physician's knowledge. It is most desirable to have a younger responsible person in charge of the drug administration as, apart from voluntary dosage reduction, old folks' memories are sometimes faulty and they become confused by the large numbers of different tablets to be taken.

Major surgical procedures are almost invariably not feasible in this age group, although Myers (1952) considered surgery should be performed irrespective of age and possible life remaining, in order to render as many as possible non-contagious. Few would agree with this view.

What of the cases in old age where the chest lesion is considered to be "healed"? On one chest X-ray it is impossible to be certain of the activity or otherwise of a lesion, and regular surveillance with sputum cultures and laryngeal swabs is desirable. Even when reasonably certain that the disease is not active, chest X-rays at yearly intervals should be arranged in view of the possibility of relapse. Furthermore, it affords an opportunity to learn of newly arrived grandchildren and offer BCG. In short, the elderly should be managed exactly as the younger patients in this respect. There is ample scope for their education in proper hygiene and this is an important reason for an initial short period in hospital at the onset of active treatment. For obvious reasons instruction and advice may meet with little response, but efforts to improve them must be made by the Health Visitor at frequent intervals by seeing them in their homes.

Some doubt exists as to the frequency of a primary infection in old age. Robertson (1953) considered this was a rare occurrence and thought reactivation of a pre-existing lesion much more common. It is significant that in this series it was not possible to trace a previous chest X-ray which was normal, although several had been X-rayed some years before the diagnosis had been established. This suggests that in most cases the lesion is long-standing.

The appearance of diseases other than tuberculosis in old age is to be expected, and Auerbach (1940) in his extensive survey of the pathology of tuberculosis in older age groups lists the various lesions found. These are substantially the same as are found in this series, with the exception of the comparatively high incidence of peptic ulceration. The association of such a variety

of diseases complicates the nursing of these patients in sanatoria and makes home treatment more difficult to arrange.

The advent of pulmonary tuberculosis in old age brings forth many problems, not the least of which is living accommodation. The wisdom of closing sanatorium beds whilst leaving these old folk at large must be questioned. A possible solution is the establishment of hostels to accommodate the elderly chronic sputum positive case.

Summary

(1) Comments are made on a series of 150 patients over the age of 65 years who had been diagnosed as pulmonary tuberculosis during the period between 1950 and 1955. The conclusion is reached that pulmonary tuberculosis in old age is not uncommon and merits the special consideration not only of geriatricians but also of chest physicians, general practitioners and public health authorities.

(2) The importance of case finding measures amongst the aged is stressed and a plea made for them to be encouraged to attend mass radiography units and be referred to chest clinics by their general practitioners.

(3) Treatment of these patients is now practicable, and with adequate chemotherapy, sputum conversion can be expected in a proportion of cases.

(4) The problem of disposal of the elderly tuberculous subject is briefly discussed and it is suggested that hostels or small disused sanatoria may be utilised for this purpose.

(5) The importance of the contact examination of old people is emphasised. It may seem unrewarding in a large proportion of cases, but if diligently pursued a surprising response may result.

REFERENCES

Auerbach, O., and Green, H. (1940): *Quart. Bull. Sea View Hosp.*, **5**, 235.
Barber, L. M., Reese, C. N., and Mazzadi, L. (1953): *Geriatrics*, **8**, 306.
Geddes, J. E., and Lowe, C. R. (1952): *Lancet*, **1**, 92.
Hartston, W. (1956): Personal communcation.
Heaf, F. R. G. (1955): *J. Roy. Inst. Publ. Hlth.*, **18**, 324.
Medlar, E. M., Spain, D. M., and Halliday, H. W. (1948): *Arch. intern. Med.*, **81**, 501.
Myers, J. A. (1952): *Geriatrics*, **7**, 324.
Robertson, R. F. (1953): *Med. ill.* (*Lond.*)., 667.
Robins, A. B. (1953): *Amer. J. Publ. Hlth.*, ii, 43, 718.
Snell, W. E. (1941): *Tubercle*, (*Lond.*), **22**, 3.
Wilkins, E. G. (1956): *Brit. med. J.*, **1**, 883.

OBSERVATIONS ON TUBERCULOSIS OF THE BREAST

REPORT OF THIRTEEN CASES

By M. Chaudhuri

From the Department of Surgery, Lady Hardinge Medical College Hospital, New Delhi

Although tuberculosis of the breast is less frequent than some other breast lesions, it is common enough to merit recognition. Owing to its ill-defined clinical features the true nature of the disease often remains obscured or is mistaken for other common conditions, chiefly carcinoma and pyogenic inflammatory lesions of the breast. These latter conditions may be difficult to distinguish from tuberculous mastitis in its various phases.

Since the earliest description of the disease by Sir Astley Cooper in 1829, a number of cases have been recorded in the literature. Recently more light has been thrown on the various aspects of mammary tuberculosis by workers in the Western countries. Shipley and Spencer (1926) reported 205 cases from the literature, Morgen (1931) reviewed 439 published cases, McKeown and Wilkinson (1952) recorded 5 cases, while Forrest and Parkes (1955) gave a comprehensive discussion on the subject. As far as I am aware no such work has been reported from India, although the incidence of tuberculosis is, on the whole, high. In view of this it is considered worth recording these personal findings, based on all the cases of breast pathology admitted to Lady Hardinge Medical College Hospital, New Delhi, in the seven years from 1949 to 1955.

Only those cases with the tuberculous lesion originating in the breast tissue and proved by histological examination are regarded as tuberculous mastitis. At times it is not easy to distinguish cases with disease spreading in to the breast from a neighbouring structure, such as through a sinus in the chest wall (Patey, 1954). Two such cases were seen but not included. In this review of 433 cases of breast pathology, 13 were tuberculous in nature according to pathological findings. Only in one patient were tubercle bacilli identified.

Report of Cases

Case 1. R.D., aged 25 years, admitted on 4.3.1949 for a mass in the right breast since delivery three years ago. The sinus had been discharging for a year, the mass had been incised twice before admission, but the condition persisted. On admission the entire breast was riddled with multiple sinuses and scars, was very indurated, and was, in fact, a destroyed organ. Simple mastectomy was performed. No other focus was detected elsewhere in the body. Histologically typical tubercle formation was found. The patient was last seen in April 1954; there was no sign of recurrence in either breast; her general condition remained good.

(*Received for publication July* 20, 1956.)

CASE 2. V.B., aged 39 years, admitted on 30.3.1950 for sinuses in both breasts following bilateral painful lumps four months previously. She had two children, the younger being 6 years old. She had had several operations on the breasts prior to admission, when she was found to be febrile with signs of a pulmonary lesion at the right apex. Locally both the breasts were nodular and firm with two sinuses on each side. The sinuses and the adjacent indurated areas were excised and a biopsy specimen was taken from a deeper part of the breasts. Histologically a tuberculous lesion was found on each side and tubercle bacilli were found in the discharge. Post-operatively, she was treated with Streptomycin and PAS; the wounds healed in three weeks. She was last seen in 1951, when the local condition was good and she was afebrile, but has not been followed up since then.

CASE 3. H.K., aged 50 years, admitted on 13.9.51 with a mass in the right breast, duration four months, discharging sinus for two months following an incision. She had four children, the last being 10 years old. Locally a small indurated mass on the medial side of the breast was found to be adherent to the deeper tissues. Its surface was ulcerated, and there was a thin serous discharge. Biopsy showed a tuberculous lesion histologically. Simple mastectomy was performed in view of the patient's age and the condition's close clinical resemblance to scirrous carcinoma. No glands were present in the axilla. Lungs were clear clinically as well as radiologically. She was seen in May 1955, having had no recurrence locally, and her general condition was good.

CASE 4. S.D., aged 30 years, admitted on 31.8.51 for a lump in the left breast for five and a half years, painful for three years. It had been incised several times before admission, initially in January 1951, when a biopsy was taken which showed a tuberculous lesion, but the patient had refused to be treated. She was readmitted eight months later with an ulcer involving the entire breast. Simple mastectomy was performed on account of the extensive nature of the lesion and the previous operations. Since then she has had two full-term deliveries with normal lactation from the right breast. She was last seen in September 1955, there was no evidence of recurrence, and she had gained 5 kilos in weight.

CASE 5. R.W., aged 21 years, admitted on 12.5.52, developed a painful lump in the right breast while nursing a three-months-old infant, duration six weeks. Local signs of inflammation were present with a small sinus close to the areola discharging pus and milk. The mass was incised, but thick caseous material was found. The entire mass was, therefore, excised and a biopsy of the adjacent breast tissue was taken. The section showed typical tubercles with giant cells. She was treated with 1 g. Streptomycin and PAS 8 g. daily for three months. When seen a year later, she was doing well.

CASE 6. B.K., aged 28 years, was seen at the out-patient clinic with a painless small mass in the lower and outer quadrant of the right breast, duration five months. It was firm, nodular, and was diagnosed as fibroadenoma. It was excised, but the histological report was a tuberculous lesion with fibrosis; no caseation was seen. She was unfortunately not followed up.

CASE 7. K.D., aged 35 years, admitted on 10.8.52 for a painful mass in the right breast, duration six months, discharging sinus for two months. She had had seven children, there was no history of breast lesion, the last child was 6

years old. Locally the right breast was more prominent than the left, with signs of inflammation and a sinus in its lower half. There was a diffuse mass, tender and soft in areas. Biopsy of the breast showed a tuberculous lesion. A few palpable glands were present in the right axilla. X-ray of the chest was normal. She was given 3 million units of Penicillin, and was then put on Streptomycin and PAS. Within four weeks the local part had healed well and she was advised to continue the treatment, but did not return.

Case 8. K.V., aged 25 years, admitted on 10.12.52 with two sinuses in the left breast, duration two years. Locally the lower half of the breast was indurated and fixed, the surface was ulcerated. A few glands in the left axilla were present. Following local excision of the sinuses with adjacent tissue a tuberculous lesion was diagnosed histologically. The axillary glands were also excised and were tuberculous in nature. No sign of pulmonary lesion was detected. She left the hospital two weeks later with the local area healed, and was put on Streptomycin and isoniazid, but was not seen again.

Case 9. J.D., 30 years old, admitted on 23.1.53 with a fixed firm mass in the left breast, duration two years, painless but gradually increasing in size. She had had three children, the youngest being 3 years old. No other focus was detected. Local resection of the mass disclosed a tuberculous lesion histologically. She was treated with Streptomycin and PAS post-operatively. The wound healed well and her general condition improved. She was last seen in September 1955, in good condition.

Case 10. P.V., aged 28 years, admitted on 9.2.54 for a mass in the left breast since her second delivery three months before admission. She was febrile in the evenings, 99 to 100. Palpable glands were found in the left axilla. Locally no sign of inflammation was present, but a soft smooth mass was palpable under the areola and was diagnosed as a galactocele pre-operatively. The mass was excised, together with the axillary glands. The section showed a lactating breast with typical tubercle formation; the lymph glands were also tuberculous. X-ray of the chest showed infiltration of the left lower lobe. Sedimentation rate was 48 mm./hr. (Wintrobe). She was treated with Streptomycin 1 g. and PAS 8 g. daily for three months. When seen six months later there was no sign of the lesion locally. She was being treated for the pulmonary lesion.

Case 11. K.L., 30 years old, had had four children; the last child was 5 years old. Admitted on 25.3.54 for a mass in the right breast of five years, duration. It was incised a year previously, but the mass persisted and became painful. On local examination it was cystic and mobile and was diagnosed as a galactocele. It was excised with the surrounding breast tissue as it was adherent. The specimen was filled with caseous material and histologically showed a tuberculous lesion. She was put on Streptomycin and PAS after the operation, continued the therapy for five months, and is being followed up. There has been no local recurrence and her general condition is good.

Case 12. B.B., aged 28 years, admitted on 22.10.54 for a painless mass in the left breast, duration fifteen days. Locally, a small nodule 1 × 1 in. in size, firm and mobile, was diagnosed as a fibroadenoma. The mass was excised and found histologically to be tuberculous in nature. Post-operatively she was

treated with Streptomycin and PAS for two months, was seen again in May 1955, when there was no sign of local recurrence.

CASE 13. R.S., aged 34 years, admitted for pain and a mass in the left breast for seven months, on September 7, 1954. She was treated for the same complaint in April 1954, and at that time pyogenic abscess was diagnosed; biopsy had shown chronic inflammatory changes. X-ray of the chest was also negative in April 1954. In September 1954, when readmitted, there was a discharging sinus at the site of the previous scar, she had a temperature between 99° and 100°. X-ray of the chest this time showed a localised lesion in the middle lobe of the right lung. In view of the findings a wedge of the affected breast was excised and the wound was closed. Histology showed a tuberculous lesion of the breast. The wound healed. She was treated with Streptomycin and PAS for three months daily, PAS was continued for two further months. She was seen in March 1956, with no local recurrence, and the pulmonary lesion had improved. She is being kept under observation.

Discussion

Incidence. In the present series the incidence of mammary tuberculosis is 3 per cent. of all cases of breast pathology. This is higher than that recorded by other workers. Gatewood (1916), from Chicago, found an incidence of 1·04 per cent., McGhee and Schmeisser (1935) recorded 1·78 per cent.; whereas Hall (1936), from St. Bartholomew's Hospital, London, reported an incidence of 1·5 per cent. in a series of 1,500 cases admitted with breast lesions. Probably the true incidence is even higher than that seen in hospital practice, as the condition is usually symptomless for a considerable period, patients do not always seek advice and may ultimately die of tuberculosis elsewhere in the body, while the breast lesion remains undetected. Sometimes on account of its variable clinical features it is diagnosed and also treated as a pyogenic lesion or even as carcinoma.

Age. In the present series the majority of patients (11 out of 13) were between 20 and 35 years of age; only one case was 50 years old (Table I). It is, therefore, a disease of younger patients as compared with carcinoma, and

AGE PERIOD	TUBERCULOUS MASTITIS		BREAST CARCINOMA	
	NUMBER OF CASES	PERCENTAGE OF CASES	NUMBER OF CASES	PERCENTAGE OF CASES
20–24 YEARS	1	7·7 %	5	4·0 %
25–29 "	5	38·5 %	6	4·7 %
30–34 "	4	30·7 %	11	8·7 %
35–39 "	2	15·4 %	6	4·7 %
40–44 "	NIL	- -	29	23·1 %
45–49 "	-	- -	18	14·3 %
50–54 "	1	7·7 %	24	19·2 %
55–59 "	-	- -	6	4·7 %
60–64 "	-	- -	10	8·0 %
65–69 "	-	- -	5	4·0 %
70–74 "	-	- -	6	4·7 %
TOTAL	13	100 %	126	100 %

TABLE I.—The incidence of tuberculous mastitis in different age groups as compared with carcinoma breast.

occurs most commonly in the period of maximum activity of the organ. In 4 patients (1, 6, 10, 11) it originated in lactating breasts (Fig. 1).

It is of interest that during the same period 126 cases of carcinoma of the breast were admitted, so that there was approximately 1 case of tuberculous

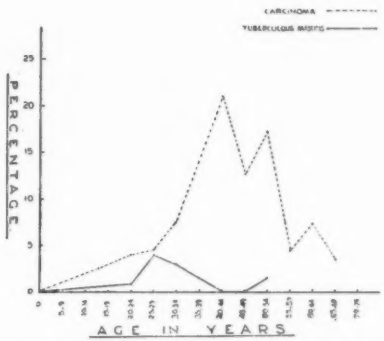

FIG. 1.—A comparison between tuberculous mastitis and carcinoma breast in different age periods in terms of percentage of total number of cases.

mastitis for 10 cases of breast carcinoma. This is a higher proportion than that recorded by Harrington (1936), from the Mayo Clinic, in a ratio of 1 : 200, the difference being mainly due to a higher incidence of tuberculosis in our series.

Sex. The present study included only women patients; it is therefore not possible to give comparative figures. It is usually regarded as a disease of the female breast. Morgen (1931), gives male to female ratio as 1 : 22. The

SIDE	NUMBER OF CASES
RIGHT	6
LEFT	6
BILATERAL	1
TOTAL	13

TABLE II.—The incidence of tuberculous mastitis on each side of the breast.

reason for its frequency in the female breast is not known, perhaps because in females the organ undergoes more frequent changes during the period of activity and is more liable to trauma and infection, thereby lowering its resistance to tubercle infection.

Its incidence was equal on both sides as in Table II. Duration of the disease when the patients were first seen varied from two weeks to five and a half years (Table III). The pathological features of the lesion are, as elsewhere in the body, typical tubercles with epitholioid cells and giant-cell formation, with or without caseation and varying degrees of fibrous tissue reaction (Fig. 2a, 2b). Pathologically two types can be distinguished—*i.e.*, (1) fibrous or scirrous type,

and (2) nodulo-caseous type (Forrest and Parkes, 1955). These types closely correspond to the clinical types which were recognised in this series. Tubercle bacilli are seldom found in the discharge or in the section of the tissue. The infection probably spreads to the breast via the blood or lymphatics, in rare cases direct from the surface via the lactiferous ducts. The lesion in the breast is always secondary to a primary focus elsewhere, commonly in the lungs and mediastinal glands.

DURATION	NUMBER OF CASES
2 WEEKS	2
3 MONTHS	1
4 MONTHS	1
5 MONTHS	1
6 MONTHS	2
7 MONTHS	1
2 YEARS	2
3 YEARS	1
5 YEARS	1
5½ YEARS	1
TOTAL	13

TABLE III.—The duration of the disease at the time of admission to the hospital.

Clinical Features

Clinically two distinct types of cases are seen: Type 1, painless localised firm mass in the breast with no other symptoms; this was found in 3 cases (3, 5 and 12). Type 2, soft cystic mass which is localised and painless at first, but sooner or later it becomes diffuse and painful with formation of abscesses which finally burst, giving rise to discharging sinuses on the surface, and ultimately the entire breast is destroyed by the disease. This type corresponds to the nodulo-caseous type pathologically.

Type 1, corresponding to the fibrous type pathologically, closely simulates neoplasms, either a fibroadenoma in the early stages or a scirrous carcinoma when seen at a later period; the mass becomes fixed to the deeper structures. In a few cases even the skin may appear tethered and the nipple retracted, thus a close resemblance may be found clinically between tuberculous mastitis and scirrous carcinoma. In some cases it may be difficult to differentiate these two conditions even at operation, and it is only by histological examination that the diagnosis is established. A solitary lump in the breast is always a doubtful lump and should be removed for microscopic examination (*Atkins*, 1951).

Type 2 cases are more frequent. In the present series 77 per cent. patients belong to this group, and only 3 of these 10 were seen in the early stages before the formation of discharging sinuses. In the early phase it may simulate any benign cystic mass in the breast, as in cases 10 and 11; diagnosis of galactocele was made preoperatively and the true nature of the lesion in each was revealed only on histological examination. In such cases diagnostic aspiration and bacteriological examination may be of value, although tubercle bacilli are not always found. Later, with sinus formation, secondary infection sets in and the bacteriological findings are not of any value in diagnosis.

PLATE XXIV

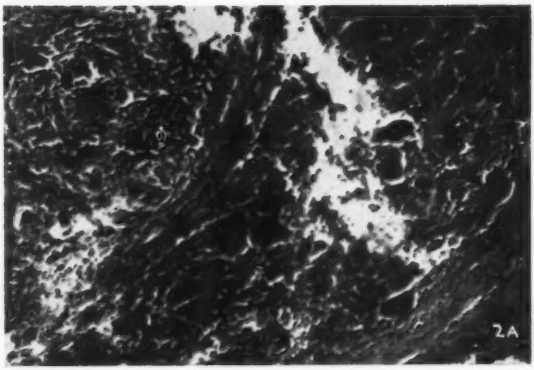

FIG. 2A.—Section showing tuberculous granulation in breast tissue in Type 2 cases.

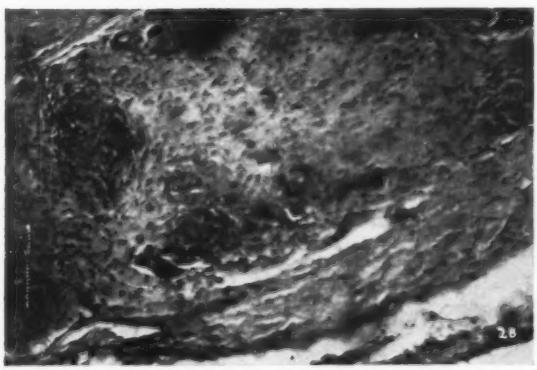

FIG. 2B.—Section showing tubercles with giant cell formation in Type 1 case, with fibrous tissue reaction.

To face p. 200

In every case it is most essential to detect the site and extent of the primary focus, and for this purpose routine radiological examination of the chest must always be done to exclude any pulmonary lesion. In others it may also be necessary to X-ray the ribs and spine to detect a primary lesion in these bones, particularly when a cold abscess is present in the vicinity of the breast.

The differential diagnosis is mainly from carcinoma in the Type 1 cases and occasionally from fibroadenoma, while in Type 2 cases it is to be differentiated from lactation and pyogenic mastitis and from other cystic masses in the breast such as galactocele. Rarely a cold abscess originating in the spine or ribs may be present in this area which may be mistaken for tuberculous mastitis. Occasionally it may be difficult to distinguish traumatic fat necrosis of the breast clinically as well as microscopically from tuberculous mastitis; in such cases it may be necessary to repeat biopsy after an interval.

Treatment

Formerly the treatment was mainly surgical, but now, with the use of new antibiotic and chemotherapeutic agents, modified and limited surgical procedure is sufficient in the majority of patients.

In the present study in the earlier group of cases, before the anti-tuberculous drugs were available, simple mastectomy was performed on 3 patients with good results. But since most of the patients are young it is best to avoid any mutilating type of operations and prevent psychological trauma. This may, however, still be indicated in the advanced cases when local resection of the diseased area cannot eradicate the disease even with the specific anti-tuberculous drugs.

In this series in recent cases, post-operatively, Streptomycin with P-aminosalicylates (PAS) was used in 7 cases, 5 of them were followed up for twelve to eighteen months with no sign of recurrence. These drugs were found to aid primary healing of operation wounds. Isoniazid with Streptomycin was used in case 1 only; this patient was unfortunately not followed up.

These anti-tuberculous drugs are effective in the treatment of tuberculous mastitis, particularly when administered in combined form. The method is found to be of value chiefly in the treatment of Type 2 cases, and when an active lesion is present elsewhere in the body in association with it. Under such conditions it is safer to avoid surgical intervention. In the present series the total amount of Streptomycin given to the patients varied from 35 to 56 g. in combination with PAS 8 to 10 g. daily for a period of three to four months. In view of the above experiences in the treatment of tuberculous mastitis the following line of treatment is considered useful:

1. In Type 1 cases and in the early Type 2 cases, local resection of the affected part of the breast with a margin of healthy tissue preferably in a wedge-shaped manner, with closure of the wound, gives most satisfactory results. If no obvious lesion is present elsewhere in the body, the anti-tuberculous drugs are not required as routine.

2. In the late Type 2 cases with multiple or persistent sinuses, surgical excision alone is not adequate and should, therefore, be followed up by combined

Streptomycin with PAS or INH therapy. This procedure gives better results than that obtained with surgery or chemotherapy alone.

3. In delayed cases with extensive lesions, as with destroyed breast, it is best to remove the affected organ by simple mastectomy. It is not necessary to do radical mastectomy in tuberculous mastitis, except in very rare cases with suspicious signs of malignancy, particularly in elderly patients. The method of choice in the majority of cases is combined treatment—*i.e.*, modified surgery with the specific anti-tuberculous drugs.

In patients with cervical or axillary adenitis and no active lesion in the lungs, excision of the glands and of the breast can be done at the same time as it was done in the case No. 10, with good results.

Summary

Thirteen cases of tuberculosis of the breast are recorded in a series of 433 patients with breast pathology admitted to the hospital. The ætiological, pathological and clinical features are discussed. Two clinical types of cases are distinguished, corresponding to the pathological types.

The treatment is discussed in the light of modern specific anti-tuberculous therapy. The indications for surgical treatment are described and the necessity for modified surgery is discussed with the result of followed-up cases.

REFERENCES

Atkins, H. J. B. (1951): *Ann. roy. Coll. Surg. Engl.*, **8,** 141.
Cooper, Sir Astley (1829): "Illustrations of Diseases of the Breast." London.
Forrest, D. M., and Parkes, R. (1955): *Postgrad. med J.*, **31,** 172.
Gatewood (1916): *Interst. med. J.*, **23,** 272.
Grausman, R. I., and Goldman, M. L. (1945): *Amer. J. Surg.*, **67,** 48.
Hall, W. E. B. (1936): *Canad. med. Ass., J.*, **35,** 520.
Harrington, S. W. (1936): *Surg. Gynec. Obestet.*, **63,** 797.
McGhee, J. L., and Schmeisser, H. C. (1935): *Amer. J. Surg.*, **28,** 461.
McKeown, K. C., and Wilkinson, K. W. (1952): *Brit. J. Surg.*, **39,** 420.
Morgen, M. (1931): *Surg. Gynec. Obestet.*, **53,** 593.
Patey, D. H. (1954): *Postgrad. med. J.*, **30,** 3.
Shipley, A. M., and Spencer, H. R. (1926): *Ann. Surg.*, **83,** 175.

REVIEWS OF BOOKS

Minimal Pulmonary Tuberculosis found by Mass Radiography. By V. H. SPRINGETT. London: H. K. Lewis. 1956. Pp. xiv+242. £2 2s. net.

The second Report of the Prophit Research Committee of the Royal College of Physicians maintains the high standard set by the first. It deals with the fate of 1,200 individuals, followed for five years, who were found by Mass X-ray Survey to have "Minimal Pulmonary Tuberculosis." This term includes patients falling into the definition of the National Tuberculosis Association of America, omitting those with cavitation, but including a few additional groups. The term is unfortunate because many of the lesions are not minimal, but as it has come into general parlance it must be accepted as defined. The material was drawn from two London Mass Survey Units, one stationary and one mobile. The yield of cases from each unit differed for some reason not clearly understood, but probably due to the superior technical efficiency of the stationary unit. This precluded the use of figures to determine the likely yield of Mass X-ray Survey in London units. A careful radiological, clinical and bacteriological examination was made in each case, and X-ray re-examinations were made at regular intervals. It was found that over 50 per cent. of cases deteriorated within five years, mainly in the first three years of the follow-up. An effort was made to discover what evidence indicated that patients were likely to deteriorate. The results confirmed statistically the impression generally held—i.e., that larger lesions, the finding of tubercle bacilli, and the presence of symptoms indicate that deterioration is likely—but show also that recent contact, a previously normal X-ray, X-ray failure to show calcification or linear shadow, and an age of less than 30 years, are also adverse indications. Deterioration in the older age group was much commoner in men. The final therapeutic results are out of date owing to advances in therapy. In view of the increasing use of Mass X-ray Surveys, results of such an investigation done with meticulous care and statistical assessment are of great value. It will be of great interest to compare them with the report, which will be published shortly, of the Brompton Hospital Survey of the fate of 1,700 child contacts followed for upwards of twenty years. A chapter is included on management based on these figures; generally speaking, little fault can be found with this, except the section on treatment. Your reviewer feels that it would have been better if this had been omitted. The evidence produced is insufficient, and from the nature of things is out of date, as is freely acknowledged. The advice is thus based only on opinions of members of the Committee. This seems out of place, tacked on to an admirable statistical survey based on carefully collected evidence. The report must be studied carefully by all those who care for tuberculous patients. This is made easy by the instructions given in the author's note telling readers how to get a bird's-eye view of the work without reading the details and statistical tables, the amplitude of which might be discouraging to some busy workers. The report does great credit to the author, and the Royal College of Physicians can be congratulated on sponsoring such an admirable production.

F. H. YOUNG.

Tuberculosis in Obstetrics and Gynæcology. By GEORGE SCHAEFER. Toronto: Little, Brown and Co.; London: J. and A. Churchill Ltd. Pp. 307. 58 illus. 63s. net.

The author of this monograph has been responsible for the care of tuberculous patients in the New York Lying-in Hospital, and has gained a large experience of the disease in two big tuberculosis hospitals. The book includes many useful lists of recent references, with full representation of British and other European work, which is sometimes overlooked by American authors.

Dr. Schaefer emphasises the fact that tuberculosis is usually a widespread disease, and that the gynæcologist can only investigate and treat the pelvic organs effectively if he has some knowledge of the problems, both clinical and social, of this infection.

A section is included on tuberculosis of the breast. The writer does not recommend breast feeding by tuberculous mothers, although he makes no distinction between active, open and other cases. Indeed, the only significant evidence that he quotes to support this view suggests that breast feeding is less harmful than is commonly supposed. The effects of pregnancy on extra-pulmonary tuberculosis are discussed, although the mechanical problems of treating a case of active tuberculosis of the spine or hip during pregnancy are not mentioned. Indications for the termination of pregnancy in cases of tuberculosis are assessed fairly and with wise conservatism. The author also sets out the different combinations of chemo-therapeutic drugs which have been tried for pelvic tuberculosis, and attempts to evaluate the incomplete evidence that has been published. Details of gynæcological surgery are not included, but the indications for this form of treatment are carefully weighed.

The book has the excellent format and illustrations that we have come to expect from North America, and it can be recommended as an authoritative and comprehensive account of the obstetric and gynæcological aspects of this disease.

S. G. CLAYTON.

Price's Textbook of the Practice of Medicine. Edited by DONALD HUNTER. Oxford University Press. Pp. 1,774. £3 3s.

The editorship of this renowned textbook of medicine, now in its ninth edition, has, through the resignation of Dr. Price, been undertaken by Dr. Donald Hunter. Its high standard as one of the foremost textbooks of its kind in this country has been well maintained, as is to be expected from contributors, both old and new, who are recognised authorities on their subjects.

In the chapters dealing with thoracic medicine, which are the major concern of readers of this Journal, it is of interest to note that the section " Diseases of the Respiratory System " by Young and Beaumont has an additional contributor in Dr. E. R. Boland. Mr. W. I. Daggett has again undertaken the section on diseases of the upper respiratory tract, and Dr. Hunter has contributed a useful chapter on the pneumoconioses. There are some who will feel that chronic bronchitis and new growths of the lung are discussed perhaps rather cursorily in view of their great social and medical significance. The section on diseases of the heart by Dr. Wallace Brigden is admirable. These sections, however, suffer from a complete absence of illustrations. Professor Clifford Wilson has given a very readable account of diseases of the blood vessels, but one cannot help feeling that the " collagen diseases," in view of their increasing clinical significance, merit a chapter to themselves. On the whole this new edition is to be welcomed as an authoritative work on general medicine and it is reasonably priced.

A Textbook of Medicine. Edited by CECIL and LOEB. W. B. Saunders Co. Pp. lxxxiv+1,786 (illus.). 105s.

The ninth edition of this well-known Textbook of Medicine is extremely comprehensive and up-to-date. The names of the contributors speak for themselves; many of them are known internationally and all are recognised authorities on their subject.

In the sphere of thoracic medicine this present edition has attempted to keep fully abreast with the rapid advances that have been made in all sections of medicine, but one is somewhat surprised to find, *e.g.* that the section on pneumonoconiosis, certainly an important subject in this country, is so scanty and deals purely with silicosis and asbestosis. Moreover, " asbestosis " is stated in the preface to be a subject which has not been covered in previous issues. There is no mention of asbestosis in the index, and having discovered it under " the pneumonoconioses " one finds this well-established disease, which has been described in this country as far back as 1927, is only briefly discussed.

The chapters on diseases of the respiratory system and cardiovascular system are, however, in the main admirably dealt with.

The book is well produced, the illustrations are on the whole good and thoracic medicine is certainly well represented.

The physician, specialised or general, should certainly have this book in his library and there is an adequate and useful bibliography at the end of each section.

PHILIP ELLMAN.

Pulmonary Emphysema. Edited by ALVAN L. BARACH and HYLAN A. BICKERMAN. Baillière, Tindall and Cox. 1956. Pp. x+535. 80s.

This book contains a vast number of interesting facts. Great stress is laid upon ventilation of the lungs and the mechanics of breathing, which are alleged to cause the chest deformity in emphysema, while relatively little importance appears to be attached to the question of infection. It is possible that the disease seen in America differs from that which is seen in this country, where it is generally felt that infection and changes resulting from this and allergic manifestations are probably the primary causes which give rise to the secondary changes in the chest. There are a number of well-known contributors, particularly on the physiological side, but the editing is deficient, with the result that there is much repetition.

The importance of anoxæmia is discussed, this being correlated with the changes found in healthy persons at high altitudes. Whether it is permissible to compare these results with those found in the emphysematous person, where the changes are due to underlying pathology, is open to question. Great importance is also attached to breathing exercises, positive pressure breathing, intermittent positive pressure breathing, etc., and the benefit derived from exercise in order to improve the fitness of the patient, giving him oxygen to enable him to do this. The value of many of these methods has not been fully established.

The chapter dealing with anti-spasmodic drugs and particularly aerosols or mists is good, and that dealing with the cortico-steroids gives a comprehensive outline of the use of these drugs, but recommends a short course with a high dosage which is not the usual practice in this country. The extra work that these patients have to do in breathing is stressed; a fact which is little appreciated by many.

The one chapter on infection is well written, bearing out the finding in this

country that *Hæmophilus influenzæ*, Streptococcus and an occasional Friedländer bacillus are the more important organisms.

The treatment of pulmonary acidosis is good.

As previously stated, while there is a lot of information in this book, the style is not easy, there is too much repetition and the authors' views as to the basic causes of emphysema are not well established.

JOSEPH SMART.

Cardiology. By WILLIAM EVANS. (2nd edit.) Butterworth. 1956. 92s. 6d.

This is the second and enlarged edition of Dr. William Evans' book on Cardiology, which is distinct from his other two works. He states in the preface that the increased size is due to the inclusion of modern methods of investigation. These are not, however, described in any detail. The arrangement, production and general appearance of the text is most attractive and there are some excellent sections, especially the chapter on the " Medico-legal Aspects " and work capacity of patients suffering from different forms of heart disease.

Dr. Evans is such an individualist that there are many unique aspects about this book. Some are remarkably sound, such as the aspects of the heart in various endocrine and neurological diseases: at other times he is at complete variance with standard opinion. The book is very readable and when such a word as valvidotomy appears, one cannot help but think that the author is something quite out of the ordinary.

RAYMOND DALEY.

Progress in Clinical Medicine. By various authors. Edited by RAYMOND DALEY and HENRY MILLER. (3rd edit.) London: J. and A. Churchill Ltd. 1956. Pp. 424. 36 illus. 40s. net.

The text in this edition has been rewritten, the chapter on Psychiatry which appeared in the previous edition has been omitted, and new chapters added on Geriatrics and Radioactive Isotopes. Subjects dealt with for the first time include the surgical treatment of heart disease, the management of hypertension, the new insulins, cortisone and corticotrophic hormones in blood disease, cervical spondylosis, carcinomatous neuropathy, the clinical aspects of disease of the adrenal glands, and the mechanism of renal failure.

In a short review it is not possible to comment on all the chapters. The book opens with a somewhat conventional account of antibiotics. The chapter on Care of the Aged, by Dr. Trevor H. Howell, is particularly well written and worth reading. Dr. Avery Jones gives us a first-class review of Gastrointestinal Diseases, especially of ulcerative colitis and steatorrhœa. Dr. Daley enlightens us in a masterly albeit somewhat didactic manner on advances made in our knowledge of Cardio-vascular Diseases. Dr. Howard Nicholson's chapter will be of particular interest to readers of this journal. In this he describes the recent work on Diseases of the Chest. Antibacterial drug treatment in pulmonary tuberculosis is fully considered—perhaps too fully. This is followed by some reflections on artificial pneumothorax, thoracoplasty and pulmonary resection. The article concludes with accounts of sarcoidosis and chronic bronchitis. The author has presented the subject in an attractive and clear manner. Dr. Henry Miller displays his customary wit and wisdom when discussing Diseases of the Nervous System. The Blood Diseases are particularly well described by Dr. Israëls. The concluding chapter, by Dr. Philip Ellman, on Chronic Rheumatic and Allied Diseases, adds a polished finish to the book.

The quality of the articles varies, as is often the case in a book to which there are several contributors; further, in several instances the same subject is considered by different writers, as exemplified by the articles on ulcerative colitis, sarcoidosis, cervical spondylosis, and the use of the cortico-steroids. This overlapping is of doubtful value. The number and nature of errors noted indicate a lack of care in proof reading. The information given is not limited to Clinical Medicine; experimental physiology and pathology and nuclear physics receive their meed of recognition. This book, however, will enable the curious reader to keep abreast of the advances in medicine during the four or five years previous to its publication.

G. E. BEAUMONT.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

Symposium of Tuberculosis. Edited by F. R. G. Heaf. London: Cassell and Co. Ltd. Pp. 755. Illus. £5 5s.

Pathological History. By Robertson F. Ogilvie. London: E. and S. Livingstone Ltd. Pp. 482. 334 illus. 52s. 6d.

Diseases of the Heart. 2nd Edition. By Charles K. Friedberg. London: W. B. Saunders Co. Ltd. 1956. Pp. xliii + 1161. Illus. £6 6s.

Chronic Bronchitis—an NAPT Symposium. National Association for the Prevention of Tuberculosis and Diseases of the Chest and Heart. London. 1957. Pp. 44 Illus. 6s.

The Registrar-General's Statistical Review of England and Wales for the year 1954. H.M. Stationery Office. Pp. 44. Illus. 6s.

A Synopsis of Children's Diseases. By John Rendle-Short. Bristol: John Wright and Sons Ltd. Pp. 624. 35s.

Le Traitement de la Tuberculose de l'Enfant. Paris: Masson et Cie. Pp. 354. 80 figs. Fr. 2,500.

Les Traitements actuels des Tuberculoses Cutanées. By Claude Huriez and Pierre H. Pelce. Pp. 124. 76 figs. Paris: Masson et Cie. 1956.

Prevention et Traitement Specifiques de la Tuberculose. By Leopold Negre. Paris: Masson et Cie. Pp. 242. Fr. 1,800.

Verso Una Vittoria Integrale Sulla Endemia Tubercolare. By G. Spaziante. Rome: La Medicina Sociale. Pp. 254. 49 figs. L. 3,000.

REPORT

UNITED NATIONS

Scientific Committee on the Effects of Atomic Radiation

The following is a summary of the statements prepared by the Scientific Committee of the United Nations set up by the General Assembly at its 10th Session.

1. The Scientific Committee on the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their general tissue, has certain undesirable effects.

2. Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources. It is possible that such radiation may be having a significant genetic effect on the population as a whole.

3. The Committee is fully aware of the importance and value of the medical use of radiations, but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source. The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject.

4. The Committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment.

NOTES AND NOTICES

EDITORIAL BOARD

Certain changes have recently been made in the composition of the Board. Dr. R. Y. Keers has recently accepted an appointment at the Cheshire Joint Sanatorium and will now be representing the Board for the Lancashire and Cheshire areas in place of Dr. Reginald Ellis who has now relinquished his duties. We are very grateful to Dr. Ellis for his past services to the Board. We also have great pleasure in welcoming Dr. Ian W. B. Grant to take the place of Dr. R. Y. Keers as our representative for Scotland. His position in the sphere of Respiratory Diseases in Scotland is well known to all workers in Thoracic Medicine.